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EXTRAGONADAL TERATOMAS

by

F. GONZALEZ-CRUSSI, M.D.

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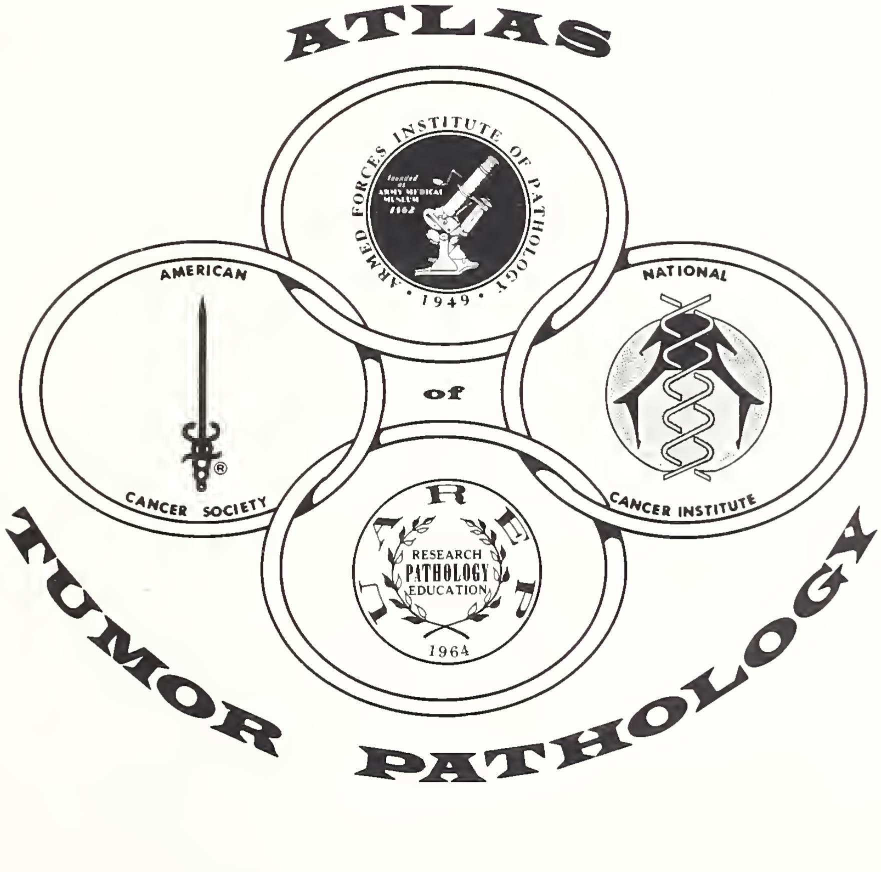
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EXTRAGONADAL TERATOMAS

by

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EDITORS' NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences—National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was done by the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 Fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final Fascicle of the first Atlas, the National Academy of Sciences—National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this series, the terminology chosen for the World Health Organization's series "International Histological Classification of Tumours" will be used when available. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information when indicated for a better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index is included in each Fascicle.

It is the hope of the Editors, past and present, the Editorial Advisory Committees, past and present, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will always be appreciated.

William H. Hartmann, M.D.
William R. Cowan, M.D.

PREFACE AND ACKNOWLEDGMENTS

The creation of a new Fascicle on Teratomas has been a manifold challenge. The original edition, coming from an illustrious pathologist and life-long student of developmental pathology, Dr. Rupert A. Willis, could not be thought of as an item to be improved. Yet, more than a quarter of a century has passed since the first edition was prepared, during which time the accretion of research activity and clinical observations has continued at an ever-quickening pace. It is a tribute to Dr. Willis' acumen that much of the volumetric gain with which the present edition is afflicted results from permutations, elaborations, and recombinations of many of his original concepts, altered on the surface, but intact in substance. It is also likely that the current swelling stems from an inability of the present author, compared to his predecessor, to couch difficult concepts into pithy and compendious phrases.

Another challenge was to keep the Teratoma Fascicle in line with the spirit embodied by its congeners. The entire series has been a justly acclaimed reference work for diagnostic recognition of tumors. Structural diversity being the defining note of teratomas, it became a particularly difficult task to decide what was "characteristic" in the morphology of these tumors. Between the Scylla of trying to illustrate the endless variations and the Charybdis of dismissing all serious attempts at graphic representation with the statement that the cells are totipotent and capable of adopting innumerable patterns, the only sensible choice was the compromise of an abstraction. It became imperative to look for common attributes among members of a set whose major defining feature is to be intrinsically variable. More than the morphologist, the basic researcher has made of this abstraction his central professional preoccupation. It was thus out of necessity that the author gravitated toward the literature on basic developmental studies. The result was an introductory section on the basic theoretical background of teratomas that seems longer than usual for the Fascicle Series. For its imperfections, the author is willing to take all just reproof; whatever deficiencies may be apparent stem exclusively from his limited grasp of a complex and rapidly expanding field. These flaws, however, do not gainsay the proposition that the chaotic and diverse morphology of these tumors can only become intelligible by the light of basic research concepts.

Still another difficulty was to avoid excessive overlap with the subject matter discussed in other volumes of the present Series. As these tumors arise in a multiplicity of sites, and as the encyclopedic zeal of other authors has been commendable, some degree of repetition could not be avoided. In particular, concepts expressed in the volumes on Gonadal Tumors and Central Nervous System Tumors will often be found echoed, expanded, or alluded to. The rightful province of teratomas is the gonads. The title of this volume implies that we have tried to characterize lesions of adventitious nature, sort of escapees incurring "extraterritorially." Their kinship to gonadal tumors, however, was not disregarded, and the most widely used classifications of germ cell tumors were held in mind, as presented by Drs. F. K. Mostofi and E. B. Price in their Fascicle.

The author insists in expressing his appreciation to Dr. William H. Hartmann, Chief Editor, for knowing how to abet without intrusiveness, and to incite without irritation. It is perhaps trite to say that this work would have been impossible without the generous contribution of illustrations by a number of pathologists. Faced with the task of illustrating lesions of extremely rare occurrence, the above statement rings true to the author in a uniquely forceful way. Accordingly, deep gratitude goes to the following contributors:

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All these colleagues generously contributed high-quality illustrations from their teaching files and publications. Dr. Jans Muller, of Indiana University, reviewed the section on intracranial teratomas; Dr. Louis P. Dehner, of the University of Minnesota, reviewed the manuscript and made valuable suggestions for its organization. Dr. Kent Mancer, of the Toronto Sick Children's Hospital, generously exceeded the duties of a reviewer and actually contributed concepts of pivotal importance to this work, such as the classification of teratomas followed in the text. The author would also like to make public his gratitude to a number of publishing houses for granting permission to reproduce copyrighted material. The origin of previously published photographs is listed on the following page.

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EXTRAGONADAL TERATOMAS

DEFINITION

Teratomas are neoplasms that originate in pluripotent cells, and are composed of a wide diversity of tissues foreign to the organ or anatomic site in which they arise.

Beyond this succinct characterization, all is controversy that surrounds the *definiendum.* It has been customary to add, as a prerequisite for the application of the term, that the presence of tissues derived from the three germ layers must be confirmed. It has also been prudently counterargued that such a demand is too exacting; full representation of ectoderm, endoderm, and mesoderm is apt to occur only in the best differentiated examples. With less advanced differentiation, the distinctive triple ancestry of the component tissues may be lacking; yet, many a tumor would seem no less a teratoma for lack of universal sanction. Lesions that include only two germ layers may bear such strong resemblance to teratomas as to render the term "heterotopia" entirely inappropriate; less extensive development of tissues does not preclude advanced differentiation.

It is therefore concluded that: (a) the multiplicity of *kinds* of tissues, (b) their topographic relationship to one another (with frequent attempts at organ formation), and (c) to the anatomic site of origin of the tumor (to which they are foreign), are what best characterize teratomas. The etymology of the term (from the Greek "teraton," a monster) suggests the notion of disturbed development. Indeed, the arrangement of tissue structures within a teratoma seems to imply attempts at reproducing — with greater or lesser accuracy — a catalog of organs found in its host, and thus reinforces the impression of the dual nature, malformative and tumoral, of these lesions.

NOMENCLATURE

In the 1951 edition of this work, R. A. Willis wrote:

"Particular tumors can be designated benign teratoma or malignant teratoma according to their structure or behavior. This is the simplest terminology and is all that is necessary."

From a practical standpoint this simple division is highly desirable, but not always feasible. Furthermore, it has been objected that the term "malignant teratoma" fails to identify the various immature tissue components that are now sufficiently recognized, and thus renders impossible a correlation between the tumor's behavior and the results of therapy (Norris et al.). Nonetheless, advocacy of terminology based on simplicity carries today stronger persuasion than it did in 1951. The names *teratoblastoma* and *teratoid tumor* Willis dismissed as clumsier and no more accurate than teratoma; *embryoma* he particularly disliked because of its implicit connotation that a teratoma represents an embryo. *Bidermoma* and *tridermoma*, denoting origin from two and three germ layers, respectively, may seem imprecise to those who question the specificity of the germ layers; at any rate, these are words seldom used today. All these terms are synonyms of teratoma; none seems to offer any particular advantage over a name already hallowed by custom. Damjanov and Solter found these synonyms generally acceptable, and felt that the word teratoma was insufficient to delineate the complex biologic and clinical behavior of these tumors. However, realizing that the medical terminology, evolved through the centuries, is no paradigm of semantic rigor, the "simplest" terminology will be followed here. The only qualification that appears necessary is the addition of a term to designate the presence of elements currently known to significantly alter the prognosis, as will be subsequently discussed. Furthermore, on the principle that proliferation of terms unaccompanied by new fundamental concepts or obvious descriptive advantage is highly undesirable, the term teratoma is to be used in preference to all the listed synonyms.

Conventional Use of Terms in Clinical Medicine

Classifications have been devised for teratomas of different anatomic sites. As their clinical usefulness has, in some cases, been tested, these classifications will be dealt with in the corresponding sections. In terms of clinical usage, no special merit is seen in detailing elaborate systematizations of a comprehensive nature, beyond the allocation of all teratomas to a benign or a malignant group, and the mention of the presence or absence of certain tissues (choriocarcinoma, yolk sac tumor) that worsen the outlook. The further qualification of *differentiated,* and *undifferentiated,* will be used here in a morphologic sense, as applied to neoplastic tissues that seem to correspond in maturity, or to lag behind in development, relative to the normal tissues of the host. We are aware that the concept of differentiation itself has been called into question, as have nearly all aspects of teratomas, and that from the standpoint of molecular biology, the primitive cellular elements of early ontogeny may be thought of as being just as highly "differentiated" as those of the adult (Manes). Nonetheless, the conventional use of these terms in the clinical literature is firmly entrenched, and their usefulness validated by experience. Accordingly, they will be preserved in this volume.

Proposed Terminology for Experimental Teratomas (Stevens and Pierce)

A vast amount of work has been carried out with experimental teratoma systems. The multiplicity of models and technics has made it necessary to invent a whole new terminology to acquaint us with the particulars of experimental teratomas: their manner of production; their salient structural characteristics; their behavior in vitro, etc. The resulting vocabulary, sometimes at odds with that of clinical medicine, has been the source of much confusion. To remedy this situation, Stevens and Pierce proposed, at a Teratoma Symposium held in 1975, the following attempt at unification of terminology.

The cells present in malignant teratomas of mice, and morphologically resembling embryonic cells, are termed *embryonal carcinoma cells.* These cells can invade and metastasize.

In the early stages of development of gonadal teratomas of mice, regardless of their ultimate benign or malignant nature, the component cells are morphologically indistinguishable from embryonic cells of the inner cell mass of blastocysts, or of ectoderm at five to six days of gestation. These cells can remain in the undifferentiated state, in which case the resultant tumor is called *embryonal carcinoma*, or become differentiated into a multitude of tissues that appear to be derivatives of the three germ layers, in which case the resultant tumor is named *teratoma*. If the tumor contains both teratoma and embryonal carcinoma components, the name applied to it is *teratocarcinoma.*

In special cases the embryonal carcinoma cells show irreversible and unidirectional differentiation into endodermal cells identical with the distal endoderm of the extraembryonic yolk sac. Such cells elaborate a secretory product that forms Reichert's membrane. Tumors so constituted are referred to as *parietal yolk sac tumors*. Once this type of differentiation has occurred, no other change appears possible. If the tumor is malignant, it may be called *parietal yolk sac carcinoma*. It appears that some of these tumors are benign, and others malignant, although the stem cells of embryonal carcinoma are not present in either. It should be noted that the profound biologic and structural differences between the human and rodent's yolk sac preclude any attempt at homologizing this tumor with so-called yolk sac carcinoma or endodermal sinus tumor of man.

A teratocarcinoma may be obtained experimentally by transplanting early mouse embryos to various anatomic sites of adult mice. The resulting tumor is indistinguishable from a spontaneously occurring ovarian or testicular teratocarcinoma, and may be appropriately called an embryo-derived teratocarcinoma.

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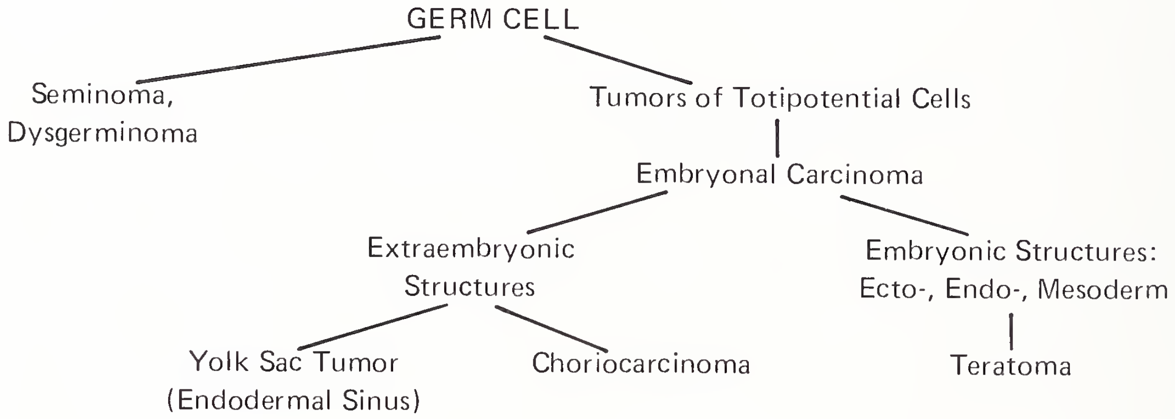
CLASSIFICATION OF GONADAL AND EXTRAGONADAL TERATOMAS

Use of Terms in Pathologic Diagnosis

As will become apparent from the review of theories of histogenesis in the following pages, the two oldest schools of thought attribute the origin of teratomas to germ cells and to undifferentiated embryonic cells, respectively. Out of these differing histogenetic concepts arose disparities in classifications that persist to our day. The early European workers generally favored the idea that germ cells give rise to seminomas and dysgerminomas, but that teratomas should be placed, along with embryonal carcinoma and choriocarcinoma, in a separate category among tumors that owe their origin to blastomeres displaced during early embryonic development, and which have escaped the influence of organizers. Opposed to this view, the classifications most widely used in North America have regarded all gonadal tumors as germ cell neoplasms. Friedman and Moore, and Dixon and Moore, in a further extension of these ideas, propounded a classification in which embryonal carcinoma of the testis was regarded as a tumor of multipotential cells with the ability to give rise to either trophoblastic cells (i.e., choriocarcinoma) or to differentiated cells of the various embryonic germ layers (teratoma). Teilum then added his concept of "endodermal sinus tumor," by which he emphasized that the embryonal carcinoma cells may also embark upon differentiation into extraembryonic structures of the primitive yolk sac. His modification of the histogenetic classification was diagrammed as follows:

GERM CELL TUMORS
(Teilum, 1965)


GERM CELL
Seminoma, Dysgerminoma
Tumors of Totipotential Cells
Embryonal Carcinoma
Extraembryonic Structures
Embryonic Structures: Ecto-, Endo-, Mesoderm
Yolk Sac Tumor (Endodermal Sinus)
Choriocarcinoma
Teratoma

Mostofi and Price, in the Fascicle on Tumors of the Male Genital System, unreservedly adhered to the view that both seminoma and nonseminomatous tumors, including teratoma, originate from germ cells. Despite their statement that documentation of this histogenesis for testis tumors is so well grounded as to render all further discussion superfluous, they carefully admitted the possibility that, under certain conditions, multipotential cells that have escaped the influence of organizers could also account for tumor formation at other sites. They systematized germ cell tumors in the following way:

GERM CELL TUMORS
(Mostofi and Price, 1973)

I. Single histologic pattern:

- Seminoma
  - Typical
  - Anaplastic
  - Spermatocytic
- Embryonal Carcinoma
  - Adult type
  - Infantile type
  - Polyembryoma
- Choriocarcinoma
- Teratoma
  - Mature
  - Immature

II. Combined histologic pattern:

Teratocarcinoma
(Teratoma with embryonal carcinoma)

Other Mixed Patterns

Different classifications of gonadal tumors allocate a specific place to teratomas in their taxonomic schemes. Their relative merits are not within the purview of this discussion. Our concern here is merely to emphasize that teratomas in extragonadal sites, regardless of their histogenesis, may coexist with tissues that display all the chief histologic patterns comprised by gonadal tumors usually classified as of germ cell derivation. Thus, the immature tissues that may be found occasionally in association with extragenital teratoma include the chief types of the Mostofi and Price classification: seminoma, embryonal carcinoma and, rarely, choriocarcinoma. (For comparison of testicular germ cell tumor classifications see Table 1.) The latter authors restrict the designation of embryonal carcinoma to lesions of distinctly embryonic, anaplastic, and epithelial appearance, adopting a number of well defined histologic arrangements. With the only qualification that the reticular and papillary pattern that Mostofi and Price subsume under embryonal carcinoma will be referred to as *yolk sac tumor* (synonym: endodermal sinus tumor) following the ideas of Teilum, all criteria for morphologic characterization of immature elements of presumptive germ cell origin found within teratomas will be the same as defined by Mostofi and Price. The implication is not a professed preference for any given histogenetic theory, but simply an attempt at terminologic unity and clarity. Experimental work on teratomas, at this time in an extraordinary upsurge, has neither invalidated the possibility of more than one histogenesis for human teratomas nor discounted the likelihood that seemingly opposed hypotheses may be found eventually reconcilable. Irrespective of what the future evolution of histogenetic concepts may be, the pathologist must be aware of the close interrelationship of morphologic patterns between teratomas and primary gonadal tumors. A practical corollary of this interrelationship is that *a gonadal primary tumor should be excluded in all cases of extragonadal teratoma,* before the latter is diagnosed as a primary neoplasm. Further discussion of the subclassification of teratomas and their morphologic attributes is given in the section of General Considerations on Human Teratomas.

The preceding considerations show the need to deal with lesions exhibiting morphologic patterns of choriocarcinoma, embryonal carcinoma, and endodermal sinus tumor. Woodtli and Hedinger have commented on the fact that the latter two lesions are morphologic equivalents, and that if the one is interpreted as teratomatous, the other should receive equal interpretation. Further grounds for the teratomatous nature of endodermal sinus tumor are as follows: (a) the same midplane anatomic sites which are preferential sites of primary teratomas are also favored primary sites for yolk sac tumor; (b) yolk sac tumors, regardless of primary site, may coexist in equal partnership with a "germ cell tumor," such as a seminoma, in a manner entirely comparable to that of teratomas; (c) typical teratomas may contain small or large foci of endodermal sinus tumor, suggesting that the latter may, on occasion, become the dominant histologic pattern; (d) the same suggestion arises from the occasional discovery of small islands of spindle cells, colonic glands (Young et al.), or squamous epithelium (Woodtli and Hedinger) in an otherwise typical endodermal sinus tumor. In view of these facts, endodermal sinus tumors are often considered to be of teratomatous nature.

Table 1

COMPARISON OF TESTICULAR GERM CELL TUMOR CLASSIFICATIONS*

DIXON and MOORE	BRITISH TESTICULAR TUMOUR PANEL†	MOSTOFI and PRICE	WORLD HEALTH ORGANIZATION‡
Seminoma	Seminoma — Classic Spermatocytic	Seminoma — Typical Spermatocytic Anaplastic	Seminoma — Typical Spermatocytic Anaplastic
Embryonal carcinoma	Malignant teratoma, undifferentiated	Embryonal carcinoma — Adult Polyembryoma	Embryonal carcinoma
Teratoma with embryonal carcinoma (teratocarcinoma)	Malignant teratoma, intermediate	Embryonal carcinoma with teratoma (teratocarcinoma)	Embryonal carcinoma with teratoma (teratocarcinoma)
Teratoma, adult	Teratoma, differentiated	Teratoma — Mature Immature	Teratoma — Mature Immature
Choriocarcinoma	Malignant teratoma Trophoblastic	Choriocarcinoma	Choriocarcinoma
—	Yolk-sac tumor	Embryonal carcinoma, infantile (juvenile)	Yolk-sac tumor

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*Adapted from Fraley, E. E., Lange, P. H., and Kennedy, B. J. Germ-cell testicular cancer in adults (first of two parts). N. Engl. J. Med. 301(26):1370-1377, 1979; and Nochomovitz, L. E. and Rosai, J. Current concepts on the histogenesis, pathology, and immunochemistry of germ cell tumors of the testis. Pathol. Annu. 13(1):327-362, 1978.

†In: Pathology of the Testis. Pugh, R. C. B. (Ed.). Oxford: Blackwell Scientific Publications, 1976.

‡From Bär, W. and Hedinger, C. Comparison of histologic types of primary testicular germ cell tumors with their metastases: consequences for the WHO and the British Nomenclatures. Virchows Arch. [Pathol. Anat.] 370(1):41-54, 1976.

Gaillard has contributed greatly toward the elucidation of the morphologic patterns adopted by this tumor. In his view, selective cloning of totipotential cells of a teratoma results in a population of cells with endomesoblastic differentiation. Because the latter cells possess a very wide range of possible morphologic cytodifferentiation, the resulting histologic appearances will be correspondingly diverse in the tumors in question; hence, it should not be surprising that the endodermal sinus tumors have generally failed to show a close resemblance to the human yolk sac, much in spite of the name "yolk sac tumor," used synonymously for these neoplasms. Hence, Gaillard is among those who believe that yolk sac carcinomas are "simplified teratomas." In his view, the tumor cells express the capacities of the perivitellin mesoblast, and recapitulate the embryonic development of early angiogenesis, without being able to reconstruct an entire simile, or "caricature" of the yolk sac. From his detailed structural studies he concludes that the ultimate histologic appearance depends on the maturity of the angioblastic elements of the endomesoblastic tumor tissue, and the relationship established between this tissue and the stromal vessels.

A comparable interpretation as "simplified teratoma" may be applied to choriocarcinoma, i.e., a tumor in which the multipotential cells (embryonal carcinoma cells) undergo differentiation toward extraembryonal trophoblastic epithelium. In contrast to the reticular appearance of yolk sac tumor, which to Gaillard is evocative of its mesoblastic origin, choriocarcinoma would display a frankly epithelial structure. Since this pattern is uncommon in extragenital lesions, only those cases in which the trophoblastic elements are clearly a part of a teratoma will be dealt with in this volume. Lastly, Mostofi and Price include with embryonal carcinoma, tumors containing organoid structures that look like early embryos (embryoid bodies) of one to two weeks' gestation. No conceptual objective exists to consider these tumors, or polyembryomas, as primitive forms of teratoma, since, experimentally, myriads of embryoid bodies are produced in the ascitic form of murine teratocarcinoma; also, the three germ layers are obviously represented in these formations (fig. 1).

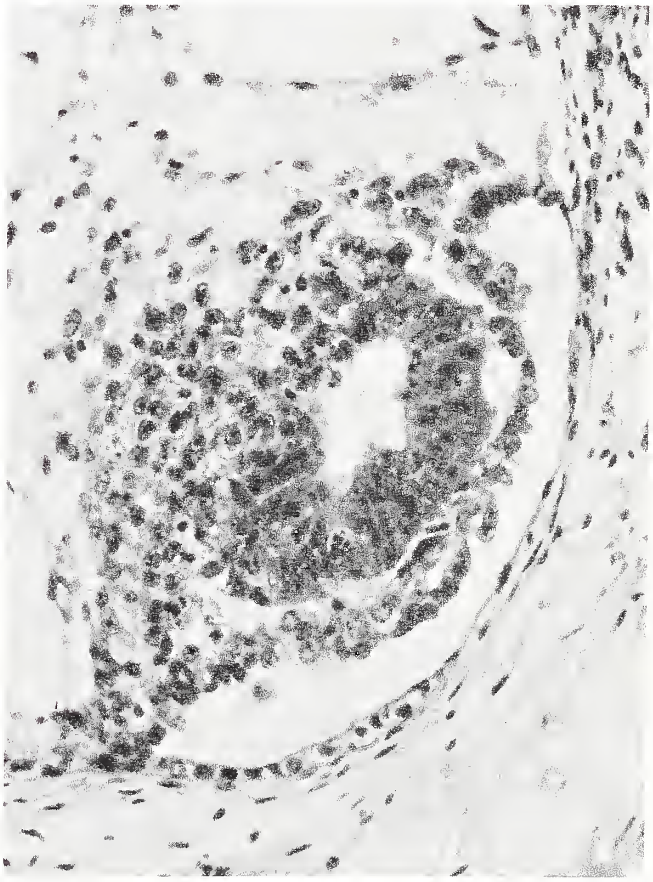

Figure 1
POLYEMBRYOMA
Histologic appearance of a polyembryoma. This tumor was constituted by numerous embroid bodies similar to the one illustrated here, each reproducing the appearance of an early embryo. (Mediastinum, 18 year old man.) Hematoxylin and eosin stain.* X790. (Courtesy of Dr. J. Gaillard, Pasteur Institute, Paris. From Peyron's original collection, section 11012-Q.)

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*Throughout the Fascicle where the stain is not so designated, hematoxylin and eosin stain has been used.

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HYPOTHESES OF ORIGIN

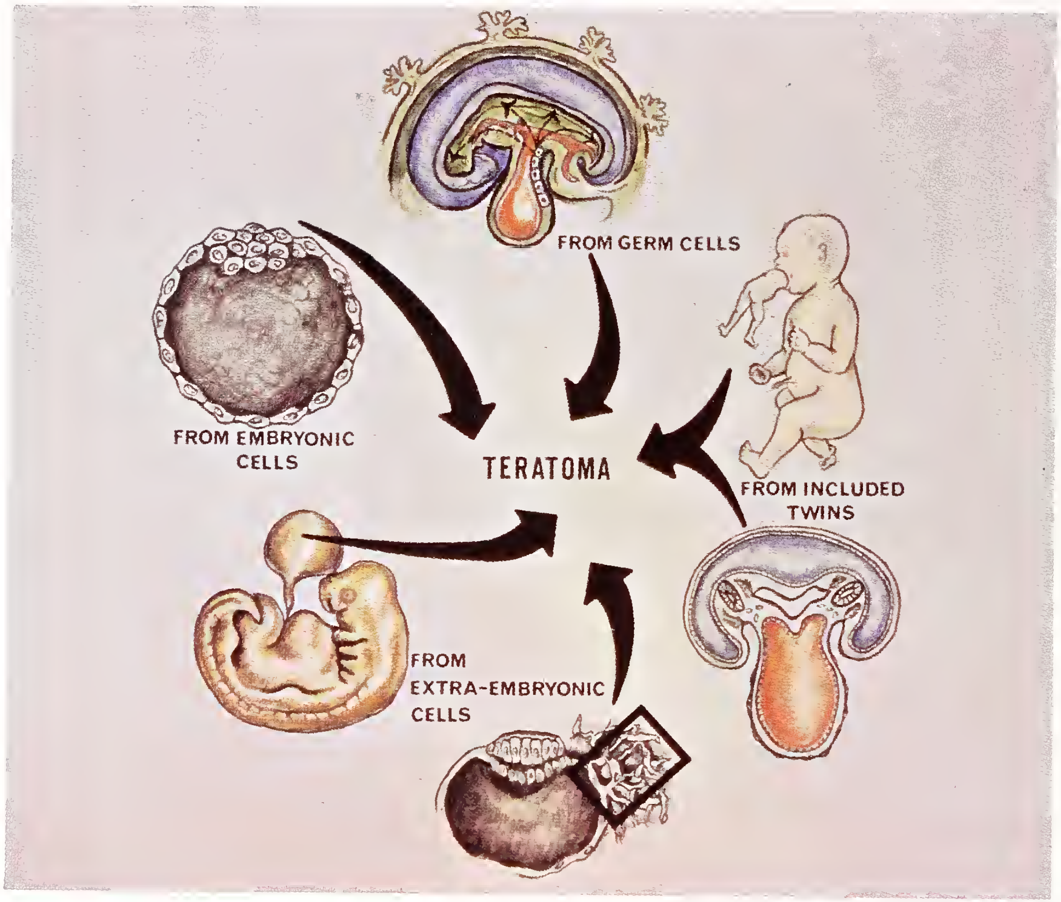
The bizarre and unusual nature of teratomas could not fail to elicit the curiosity of countless investigators. Accordingly, a large number of theories have tried to explain the histogenesis of these tumors. For some, an imposing array of evidence already exists. Others, highly speculative, or as bizarre as the tumors they meant to explain, are now of purely historical interest. For convenience, modern theories on the histogenesis of teratomas may be divided into those that claim that these tumors originate: (a) from primordial germ cells; (b) from nongerminal cells of the early conceptus, or "embryonic" cells; (c) from extraembryonic cells; (d) from "stem cells" that, regardless of the location and pathogenesis of the tumor, may be considered mutually equivalent or identical; (e) from "included," i.e., conjoined and maldeveloped, twins; (f) from different cell types, and possibly by different pathogenesis depending on the anatomic site or origin of the teratoma (pl. I-A).

The Germ Cell Theory

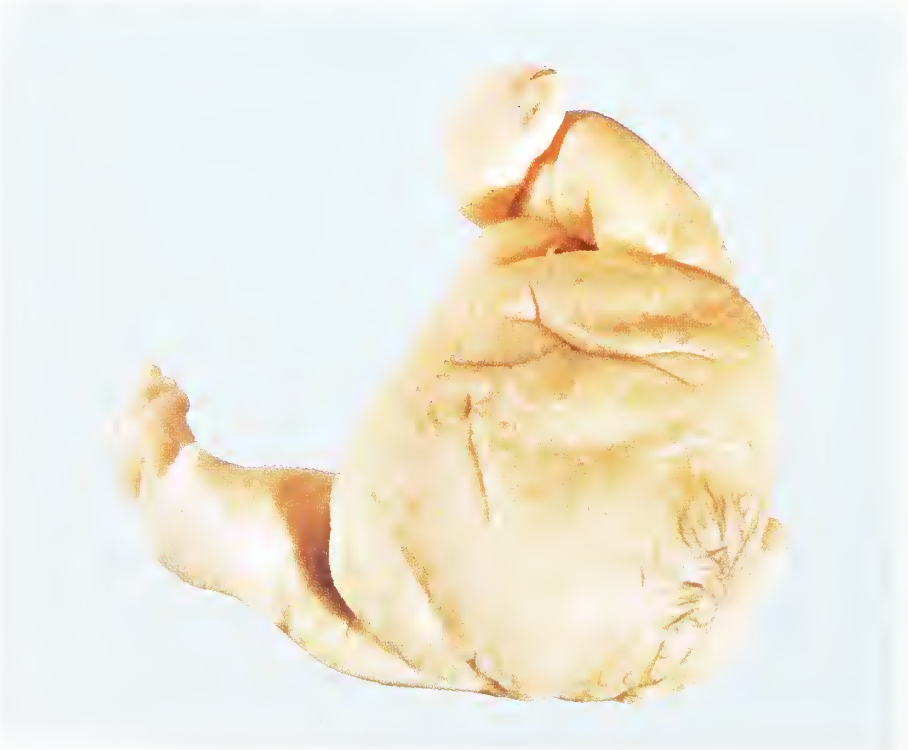
It is accepted that the fertilized ovum, or zygote, differentiates during early embryonic life into three major cell lines: (a) the somatic cell line, represented by the blastoderm that cleaves into ectoderm, endoderm, and mesoderm, and which will eventually form the individual itself; (b) the extraembryonic cell line, represented by extraembryonic tissues, trophoblast, and yolk sac, whose main function is to nourish and support the developing individual; and (c) the germ cell line, to which is delegated the function of perpetuating the species. New concepts in cellular biology may seem to challenge these principles, but there is no coherent body of evidence to replace the embryologic doctrine of early segregation of embryonic cells into three differently oriented cell lines. Of these, the germ cell line has a unique place, as it appears to be the sole repository of the largely unknown biologic mechanisms that make possible the preservation of the species. It is the progenitor cell of all other cells, which have been regarded as "the tools of the germ cell line" (Beard). This viewpoint, undoubtedly slanted with a strong teleologic bias, is embodied in the colorful expression that "the individual is merely a 'trustee' for the cells that maintain the species" (Mulligan). According to this idea, the fertilized egg divides into the cells that compose the individual, and cells that remain unchanged, but which contribute to the formation of a new individual. The latter cells would have to be "totipotential"; consequently, it is not surprising that the origin of teratomas has been closely linked with germ cells. A recapitulation on some characteristics of germ cells is therefore appropriate.

Primordial germ cells, also referred to as gonocytes (Hamilton and Mossman) because they subsequently give rise to all the sex cells of the organism, first become identifiable as interspersed elements in the yolk endoderm. Early segregation of primordial germ cells from their surrounding endodermal neighbors occurs in most species. By active ameboid movements, probably controlled by chemotactic influences, germ cells gain the body of the embryo proper, and reach the site of the future gonad. In some birds, they may

PLATE I



A. THE HYPOTHESES OF ORIGIN OF TERATOMAS



B. FETUS-IN-FETU
(Plate I-B and figures 5 and 6 from same case)
"Fetiform" gross appearance of the excised mass.

enter the body of the embryo via the blood stream (Hamilton and Mossman). Descriptive studies in human embryos during the first half of this century defined a restricted area of the yolk sac, close to the allantoic diverticulum, as the site of origin of germ cells (Fuss; Hamlett; Stevens). Whether these cells form in the endoderm, or whether having originated elsewhere (for instance, in the adjacent splanchnopleural mesoderm) they secondarily penetrate the endodermal layer, is still undecided. Recent ultrastructural observations in the mouse embryo suggested that primordial germ cells might originate outside the endoderm (Clark and Eddy). Whatever the case may be, even in presomitic embryos, the primordial germ cells may be identified by light microscopy as cells distinctly larger than the surrounding mesenchymal and endodermal cells; their nucleus is vesicular, and their abundant cytoplasm less eosinophilic than that of adjacent cells. Light microscopic identification is facilitated by these features, and by a positive alkaline phosphatase reaction (Chiquoine; McKay et al.). The alkaline phosphatase activity resides mainly at the plasma membrane; as is the case for other enzymes, it is concentrated and "packaged" at the Golgi apparatus. This enzyme has an important carbohydrate component moiety (Fishman and Ghosh), which is added to the enzyme in the Golgi region of the germ cell.

Thus, it has been possible to trace the origin and to follow the migration of these cells in the embryo. By the nineteenth day of gestation germ cells become incorporated in the hindgut of the embryo, whence they migrate along its mesentery to the gonadal ridge. In human embryos of 4-5 mm. crown-rump length the gonadal, or genital ridges, appear as thickenings of the coelomic epithelium on the medial aspects of the mesonephros. These ridges appear distinct when the coelomic lining cells of this region acquire the appearance of an epithelium. Soon thereafter, cords of cells proliferate from the epithelium into the mesenchyme. At this point, the future gonads are essentially made up of coelomic mesodermal cells that have penetrated from the superficial epithelium, but at the end of the fourth and beginning of the fifth week of gestation the large primordial germ cells settle in the gonads. Germ cells are then called oogonia or spermatogonia. Although at one time it was debated whether germ cells originated within the gonad, or in extragonadal sites (Everett; Nieuwkoop), it is now established that germ cells originate in the yolk sac, and reach the future gonad by active ameboid movements. Recent studies have dealt with the ultrastructural characteristics of primordial germ cells in the rat (Eddy; Eddy and Clark) and in the mouse (Clark and Eddy; Witschi). These cells increase in size, from an average of 12μ in diameter at the time of their residence in the yolk sac, to an average of 14μ by the time they reach the gonadal ridge (Clark and Eddy). Together with volumetric increase, there is greater organelle complexity with time, suggesting a progressive evolution of metabolically active cells formerly unappreciated by light microscopic studies. Dense-cored vesicles of uncertain function have served to identify these cells during early stages of their migration (Clark and Eddy; Eddy and Clark).

Contemporary molecular biology provides a rational basis for the proposition that all cells may contain the necessary information for the creation of an entire individual. This staggeringly complex information is condensed in the base sequence of nuclear DNA. However, under normal circumstances in mammals, this unique attribute is restricted to gametocytes after fertilization. Hence, the conclusion seemed justified that the mechanisms for multifarious differentiation are primarily contained in, and expressed by, the germ cell line. Accordingly, germ cells seemed good candidates to account for tumors composed of tissues as diverse as are seen in teratomas. The migratory capacity of germ cells also provides a convenient way to explain the occurrence of teratomas in a variety of anatomic sites. The distances that need to be covered are, in the embryo, a matter of micra or millimeters. Neither the preferential distribution nor the occurrence of these tumors in sites remote from the purported origin of germ cells are objections to this theory. Experimental work and clinical observations have added considerable weight to this concept of histogenesis. Some of the arguments in favor of the germ cell theory of origin of teratomas may be summarized as follows:

1. The well known tendency of teratomas to originate within the gonads, where, collectively, they are more common than at any other site.
2. Extragonadal teratomas generally occur on a median, or close to median location, in keeping with the origin and migration of germ cells in the embryo.
3. Incipient experimental teratomas were shown by Stevens to appear as minute neoplasms confined to the interior of seminiferous tubules, where the only possible progenitor cells are germ cells or Sertoli cells.
4. In man, a possible counterpart to the experimental observation just cited is the occurrence of foci of cytologic anaplasia ("in situ" change) in germ cells of seminiferous tubules adjacent to a testicular teratoma (Skakkebaek). Prospective studies have supported the malignant nature of such intratubular atypical germ cells (Skakkebaek).
5. Teratomas are produced experimentally from male genital ridges of mouse embryos of 11-13 days of gestation grafted into the testes of isogeneic adult recipients (Stevens, 1967).
6. There are strains of mice that, because of their genetic constitution, develop fetal genital ridges that are very poor in germ cells. When these ridges are grafted into adult recipients, they fail to form teratomas (Stevens, 1964, 1967).
7. Chromosomal and biochemical data discussed in a separate section (see Cytogenetic Data) indicate that the presence in teratomas of chromosomal markers and enzymes controlled at specific genetic loci are compatible with origin of some types of human and experimental murine teratomas from diploid germ cells.
8. Ultrastructural data indicate that primordial germ cells of fetal mice and embryonal carcinoma cells of experimentally induced murine teratocarcinoma are morphologically indistinguishable (Pierce and Beals).

The evidence is impressive that attributes the origin of experimental teratomas to germ cells. Several problems, however, remain to be clarified with respect to spontaneously occurring human teratomas. Firstly, the degree to which findings in experimental animal models may be transferred to the human species needs to be better defined. Secondly, different clinical characteristics of teratomas of dissimilar sites of origin pose the question whether a single theory of histogenesis is universally applicable to all these tumors. Thirdly, even assuming the validity of germinal origin, a considerable amount of work is required before the mechanism that controls the inception of these tumors is understood. As will be discussed subsequently, direct origin from primordial haploid germ cells appears unlikely. Thus, it remains to be explained in what way does the activation of the nuclei of primitive sex cells take place. Cytoplasmic or extraneous influences might act as "nuclear activators" to induce parthenogenesis in one or more cells of germinal ancestry, perhaps before the reductional division of the germ cell. Obviously, investigation of these phenomena goes beyond the elucidation of the histogenesis of teratomas, and merges with fundamental questions of cell differentiation.

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The "Embryonic Cell" Theory

This theory states that foci of plastic pluripotential embryonic cells may escape the influence of the primary organizer during early embryonic development, and give rise to teratomas. In 1967, Stevens could write that no direct evidence existed in support of this theory, and that several facts spoke against it, namely: predominance of gonadal primary site; distinct sex preference of teratomas in different animal species; laterality preference (right-sided) of murine and human testicular teratocarcinoma; and experimental gonadal induction in animals. Since then, it has been clearly shown that, at least experimentally, embryonic cells may give rise to teratomas. Credit went also to Stevens for affording initial proof of this hypothesis. The original hypothetical and experimental considerations, however, can be traced to Askanazy of the University of Geneva, at the beginning of the present century. Damjanov and Solter have reviewed even earlier theories of visionary observers who suspected that "displaced blastomeres," i.e., groups of primitive embryonic cells, may elude the controlling influences of inductors or organizers and become the origin of teratomas. Some of the arguments of this theory may be formulated as follows:

1. Spontaneous teratomas do not occur exclusively in the gonads, and may arise in sites that show no propinquity to the fetal gonads.
2. Teratomas may be produced experimentally by transplanting ectodermal cells of early mouse embryos (up to the seventh day of gestation) in the prestreak stages, before any germ cells are recognizable, into the testicle of isogeneic mice (Damjanov and Solter; Diwan and Stevens; Stevens, 1968, 1970). The recipient animals need not be immunologically deficient. Contrary to expectations, recipient animals with deficiency of cell-mediated immunity appear to be "protected" against the development of embryo-derived teratomas, and when teratomas develop, they are almost always benign (Solter and Damjanov).
3. Since the initial transplantation experiments were carried out into the testes, it could be argued that the germ cells of the host, not the grafted embryonic cells, were the origin of the tumors. This possibility was discounted when Dunn and Stevens showed that the karyotype of the embryo-derived teratocarcinoma was sometimes male and sometimes female. Further confirmation was obtained by producing teratocarcinomas with grafts placed under the kidney capsule of histocompatible recipients.
4. The C_3H strain of mice has no capacity to form teratocarcinomas when fetal genital ridges of these mice are transplanted into appropriate recipients, indicating lack of teratocarcinogenic cells. However, embryonic cells of the same strain of mice are able to produce teratocarcinomas when transplanted into appropriate recipient sites (Damjanov and Solter).
5. Some experimental evidence indicates that germ cells are particularly labile, and are unable to survive in extrauterine sites (Ozdenski). Grafts of embryos beyond the eighth and ninth day of gestation, already containing germ cells, are notoriously incapable of producing teratocarcinomas (Damjanov et al.). Earlier mouse embryos regularly produce teratocarcinomas.
6. Morphologic study of early embryos grafted into the testis of appropriate recipients fails to disclose any clusters of germ cells. This observation militates against the possibility that embryonic cells first differentiate into germ cells, and then give rise to a teratoma. Instead, it is suggested that the embryonic cells themselves constitute the origin of the tumor.
7. Embryonic cells of mice lose their capacity to form teratomas and teratocarcinomas when transplanted after the eighth day of gestation. Loss of teratocarcinogenetic potency closely correlates with certain events of embryonic development, notably beginning eversion

of the egg cylinder, and formation of the primitive streak. This suggests that coincident with these phenomena, the ''programming'' of differentiation becomes so firmly imprinted on embryonic cells that they can no longer remain as "undifferentiated" cells to become the stem cells of teratocarcinoma. Indirectly, the existence of such a sharply monitored temporal mechanism provides occasion to hypothesize that, under abnormal circumstances, foci of embryonic cells escaping the controlling mechanism could retain their undifferentiated state and produce a tumor, as proposed in the "displaced blastomeres" hypothesis.

8. A number of biochemical, morphologic, and immunologic similarities exist between embryonic cells and the stem cells of experimental teratomas, i.e., embryonal carcinoma cells. Some of these will be discussed later (see Properties and Behavior of Teratomas in vitro). However, a fundamental difference persists, namely: the malignant nature of embryonal carcinoma cells, which is apparently transmitted to many cell generations. Accordingly, Martin predicted that the most critical test of the idea that embryonal carcinoma cells are, like normal embryonic cells, multipotent, would be to demonstrate that when embryonal carcinoma cells are placed in the appropriate environment they can give rise to a complete, new individual. In other words, it was required to show that the parent cells of teratomas are not necessarily malignant, but that their malignant properties are reversible and may be exchanged for the normal orderly differentiation of nonneoplastic cells, given the appropriate set of controllable conditions. Indisputable proof of this

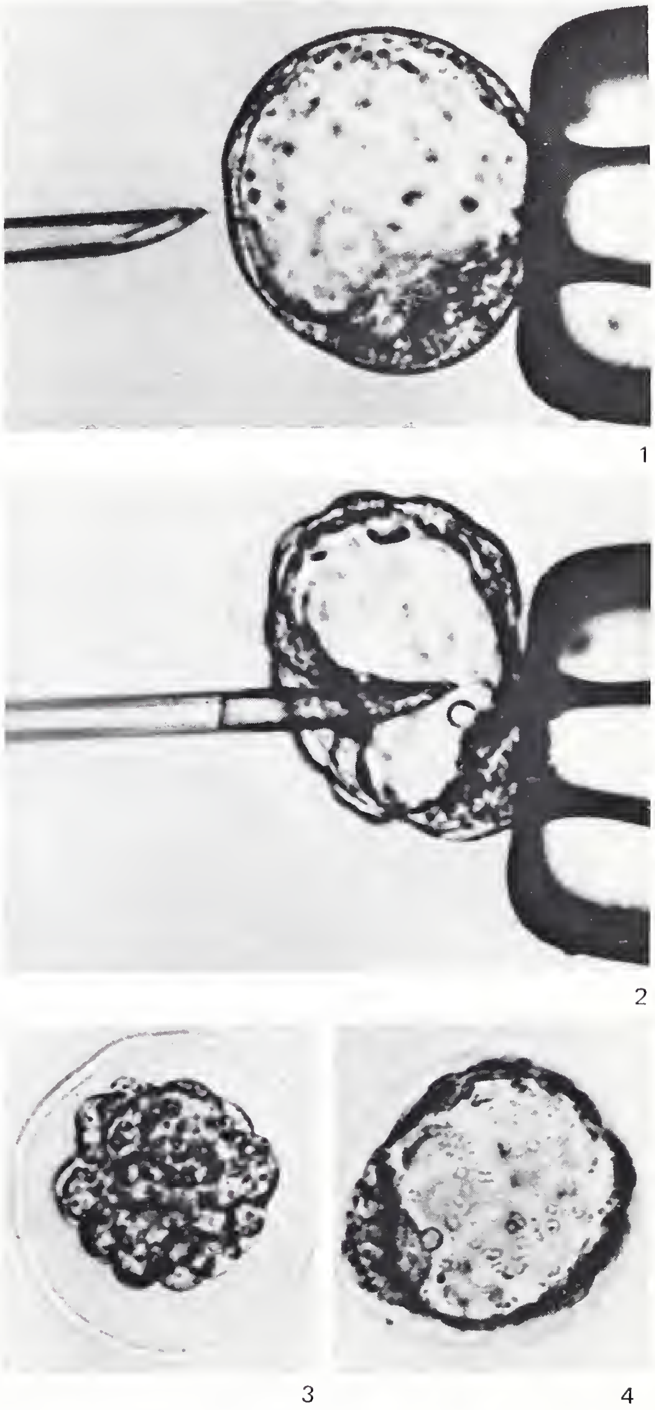

Figure 2
EXPERIMENTAL PRODUCTION OF TERATOMAS

A single embryonal carcinoma cell (1, upper photo) from an experimental tertocarcinoma is injected into a 4½ day old blastocyst (2, middle photo) fixed to the end of a blunt pipette. The blastocyst temporarily collapses (3, lower left) after the microsurgery. Later, it expands and the injected cell is retained in the inner cell mass (4, lower right), to which it incorporates. A "grafted embryo" of this kind can grow inside a foster mother to produce a chimeric mouse. (From Illmensee, K. and Stevens, L. C. Teratomas and chimeras. Sci. Am. 240(4):120-132, 1979.)

pluripotency has now become available. The work of many investigators, notably Gardner, Brinster, Illmensee and Mintz, culminated in this conclusive demonstration. Embryonal carcinoma cells, including *a single* cell, have been injected into the inner cell mass of a recipient blastocyst, which was then implanted into a foster mother. Growth proceeded to term, producing mice whose somatic characteristics partake of the phenotypes of the donor and recipient cells (chimerism). This extraordinary experimental achievement opens a number of possibilities for the future study of neoplasia and differentiation processes. The observation that germ cells are probably derived from embryonal carcinoma cells has been one of the striking preliminary findings resulting from this approach (McBurney), although conclusive proof of this is still lacking (figs. 2–4).

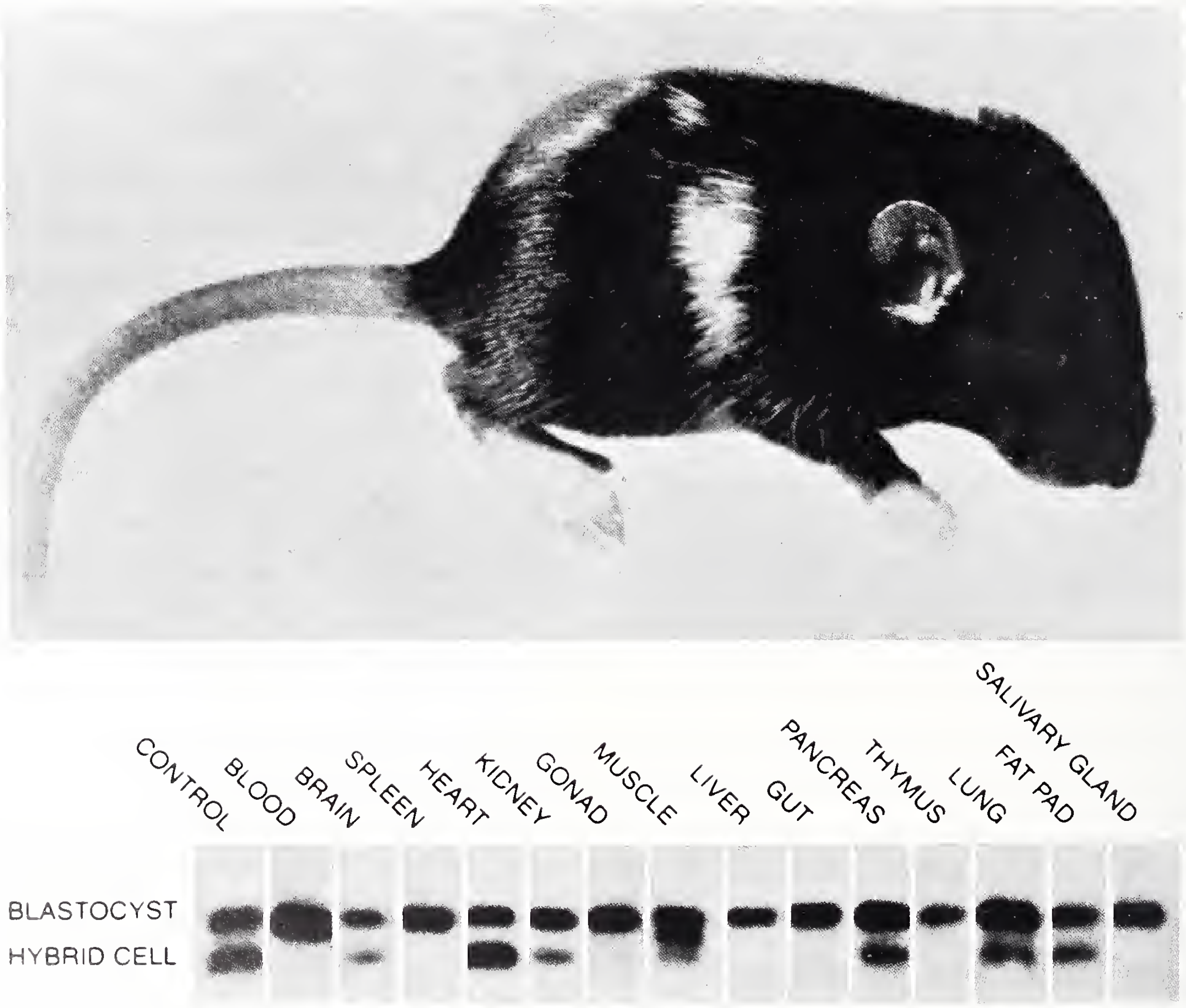

Figure 3

EXPERIMENTAL PRODUCTION OF TERATOMAS

Chimeric mouse obtained by the injection of a hybridized mouse-human cell into a mouse blastocyst. The white patch is derived from the injected hybrid cell. The black coat corresponds to the blastocyst strain that received the graft. The starch electrophoresis strips at the bottom compare the mobility of glucose-phosphate isomerase from various tissues. In seven tissues there is a slow-moving enzyme variant, proving the functional state of the hybrid-cell enzyme in the chimera. (From Illmensee, K. and Stevens, L. C. Teratomas and chimeras. Sci. Am. 240(4):120-132, 1979.)

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The "Unifying" Hypothesis

In the opinion of Damjanov and Solter, the two precedingly discussed hypotheses need not be irreconcilable, and may be brought together under a unifying concept. As stated by these authors: "The main contention of the unifying concept is that the stem cells of all teratocarcinomas, irrespective of their origin and mode of production, are basically equivalent, not to say identical."

The evidence cited by these authors in support of this contention includes:

1. Histologic and ultrastructural resemblance of germ cells, embryonal carcinoma cells, embryo-derived teratocarcinoma cells, and normal embryonic cells of the mouse egg cylinder that contain the progenitor cells of embryo-derived tumors (Damjanov et al.; Pierce and Beals; Pierce et al.).
2. Histochemical similarity of ectodermal and mesodermal embryonic cells, primordial germ cells, and ancestral cells of teratocarcinomas, all of which display strong alkaline phosphatase reactivity (Solter et al.).
3. A number of immunologic properties have been recently shown to be common to murine teratocarcinoma cells, germ cells, and normal cells of the early mouse embryo. These include the expression of certain surface antigens. For instance, F9 is present on embryonal carcinoma cells, on normal embryonic cells up to day 10 of gestation, and on male (although not female) germ cells (Gachelin).
4. Criticism of the concept of "neoplastic transformation" on the grounds that germ cells, or embryonic cells, are assumed to undergo an undefined change before proliferating to become tumor cells. The lack of precision surrounding the alleged "transformation" overlooks the possibility that a number of "equivalent cells" could generate a teratoma when controlling local factors fail. Thus, germ cells or normal ectodermal cells might, according to Damjanov and Solter, undergo unrestrained proliferation as an expression

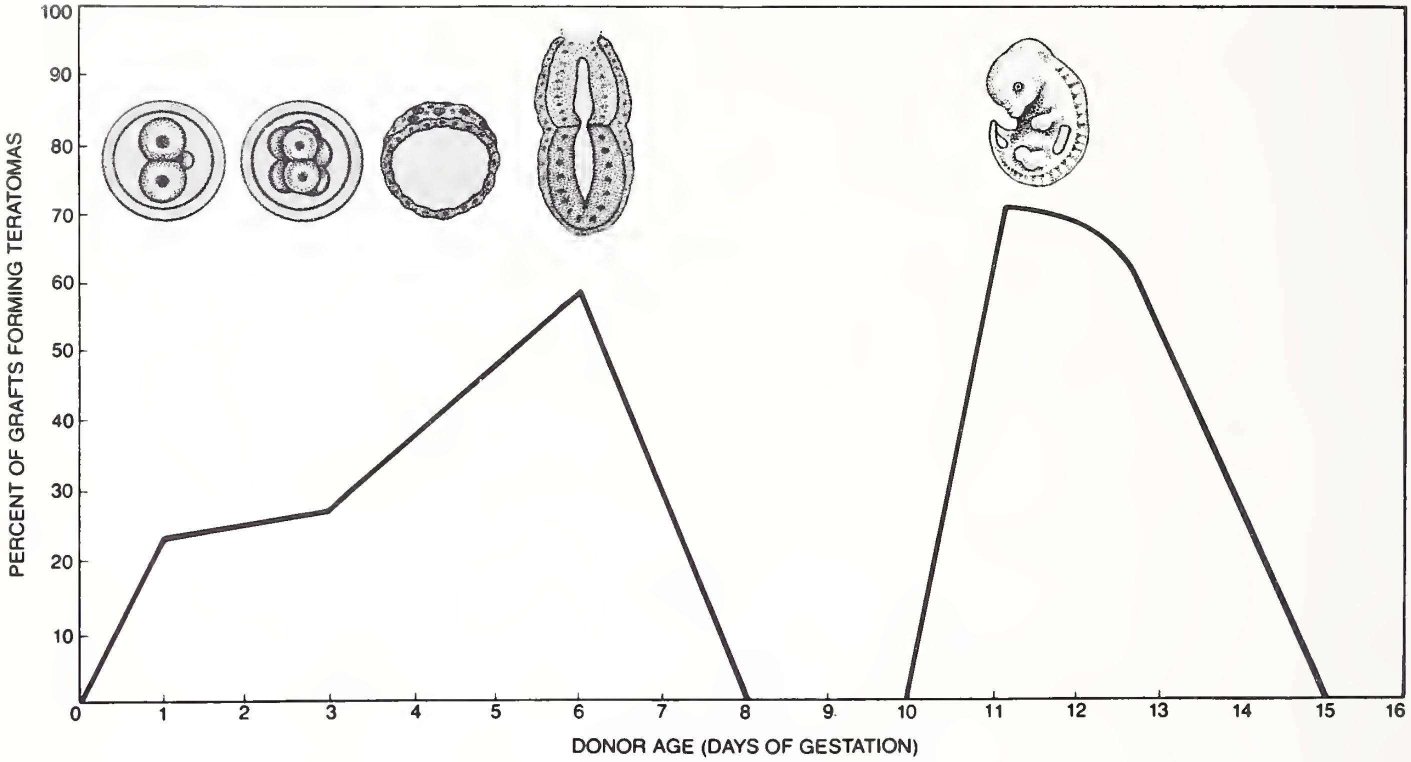

Figure 4

EXPERIMENTAL PRODUCTION OF TERATOMAS

Experimental methods for the production of teratomas in the mouse, and their results. Implantation of early conceptuses (left), or of the genital ridge of an older embryo (right), into an appropriate recipient, produces a teratoma with the degree of reproducibility shown in the graph. (From Illmensee, K. and Stevens, L. C. Teratomas and chimeras. Sci. Am. 240(4):120-132, 1979.)

of their normal (but extraneously restricted) potentialities, as soon as the appropriate conditions appear.

The latter hypothetic concept pervades much of the work of researchers in the field of teratoma. Since cloning and transplantation experiments with this tumor often result in teratoma formation *without* any of the traditionally used tumorigenic stimulation, it seems natural that investigators in this area should be influenced by the concept of neoplasia as "continued development," that is, a form of normal development that is apt to occur under certain conditions, without invoking a fundamental but vaguely defined intrinsic transformation. The murine teratoma experimental model provides abundant amounts of cells which are at the same time malignant and capable of losing their malignant properties, and of engaging extensively in tissue differentiation and embryogenesis when their environment is suitably modified (figs. 2–4).

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The "Extraembryonic Cell" Theory

In 1973, Vandeputte and associates described the induction of rat tumors in utero by murine sarcoma virus. Among the tumors so induced, they noted two cases in which the metastases contained areas of embryonal carcinoma, carcinosarcoma, and yolk sac carcinoma. It was then suspected that the primary tumors, which had been classified as yolk sac carcinomas probably derived from the parietal yolk sac, contained multipotential cells capable of differentiation. Previously, Payne and Payne had afforded evidence that the visceral layer of the rodent's yolk sac, when ectopically implanted, is capable of differentiation. These facts led Sobis and Vandeputte to investigate the differentiation capacity of the fetal membranes under experimental conditions. Their findings are of particular relevance to the histogenetic theories of teratomas, and favor origin of these tumors from displaced visceral yolk sac. Some of the data and speculations stemming from this work may be summarized as follows:

1. When fetuses of rats of the inbred R strain (Wistar albino) are removed from the uterine horns, and the visceral yolk sac is left hanging through the fetectomy incision for several weeks, a benign teratoma develops at this site almost invariably (19 out of 20 cases) (Sobis and Vandeputte, 1974). In hamsters, the teratomas produced by this experimental method are sometimes malignant (Sobis and Vandeputte, 1977).

2. The primordial germ cells have migrated from the yolk sac of the rat by the 9th or 10th day of gestation. Since the experimental procedure described was carried out in 12 day old conceptuses, it is unlikely that yolk sac-derived teratomas are of germ cell origin.

3. The visceral yolk sac is composed of endoderm and mesoderm; yet, the tissues present in teratomas obtained from displaced visceral yolk sac show derivatives from all three germ layers, including skin and nervous tissue.

4. Trophoblast, embryonal carcinoma cells, early embryonic structures, or undifferentiated embryonic cells were not observed in a morphologic sequential study of the development of yolk sac-derived teratomas (Sobis and Vandeputte, 1975). This stands in sharp contrast with the known progression of embryo-derived teratomas and teratocarcinomas (Stevens), and suggests a different mode of origin and different cellular ancestry for yolk sac-derived teratomas.

5. Further proof that yolk sac-derived teratomas are not of germ cell origin was obtained when it was shown that these teratomas develop unimpeded by busulphan administration (Sobis and Vandeputte, 1976). This drug is known to selectively destroy primordial germ cells (Hemsworth and Jackson), and would be expected to interfere with the development of teratomas of the yolk sac if such cells were the progenitors of these tumors.

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The "Included-Twin" Hypothesis

The striking organotypic differentiation that is present in some teratomas has suggested the possible origin of these tumors from a twin fetus that would have become "included" or incorporated in its co-twin, through some embryologic mishap. As Nicholson stated: "There are two ways of regarding a teratoma: as an aborted organism that has failed, to use a popular figure of speech, to produce an orderly soma, or as a malformation that has partly succeeded, creditably on the whole, in producing a number of somatic tissues. In the former view the teratoma is analogous to the double monsters, in the latter it is relegated to the hamartomata or tumors." The presence of complex structures in teratomas such as complete digits with bony phalanxes, skin and nails, and mandible with teeth implanted on alveolar sockets, is at times very impressive. No less impressive is the developmental timetable to which these structures appear subject: successive teeth have "erupted" sequentially in an ovarian teratoma that the patient refused to have excised (Wollin and Ozonoff). Furthermore, some examples of teratomas have shown well differentiated complex structures that were deemed to be of the same "age" as the host. The older terminology, *teratomata coetanea,* or "coetaneous teratomas" seemed to be particularly apposite (Masson). From these observations arose the facile interpretation of teratomas as "independent" blighted fetuses.

Nicholson's "Studies on Tumor Formation" were largely devoted to a systematic refutation of the claims that certain examples of teratoma represent "rudimentary fetuses." These studies, later collected in a single volume, may be consulted for details regarding the anatomic structure of many instances of teratomas originally reputed to be "rudimentary" or blighted twins. In every case an attempt was made to homologize the teratoma with a normal embryo, on the one hand, and with a solid teratoma, on the other hand. In every case Nicholson concluded that any similarity between teratomas and fetuses is purely external, and that the proposition that teratomas *are* fetuses cannot be accepted as valid. Structural similarities may not be equated to identity, and on these grounds true "fetiformity" was denied to the most striking examples. He subscribed to the idea that no objective evidence exists for the belief that teratomas, no matter how faithfully they reproduce complex structures, can be identified with "rudimentary human beings" of simultaneous conception, i.e., blighted twins. Since the early part of this century, two main criteria have been followed for distinction between teratomas and blighted fetuses. Firstly, teratomas are characterized by an inherent power of proliferation that, as true tumors, they share with other neoplasms. Secondly, a vertebral or notochordal axis is lacking in teratomas, whereas "included fetuses" should display at least an intimation of somatic axis, usually an imperfect vertebral column that allows the discernment of symmetry. These two characteristics have been taken as key features that permit a hard and fast distinction between the two conditions under discussion, in spite of occasional references to the "skeletal" complexity of some teratomas (Ashley; Plaut). Masson quotes a case described by Plaut of an almost complete skeleton in a teratoma. It is doubtful, however, whether such isolated instances would stand as close a scrutiny as Nicholson applied to some older reports.

Structural considerations aside, the concept of teratomas as "included fetuses" is still entertained on the basis of epidemiologic observations. From a study of stillbirths with congenital anomalies in England and Wales, Rogers (1969) concluded that the rarity of twins concordant for anencephaly or spina bifida might be due to the fusion or destruction of one of the twins, so that only one survives to be born with the congenital anomaly. Knox further postulated that dizygous twins may interact in such a way that one twin disappears completely while the other one is born with anencephaly. Rogers (1976) amplified his views, noting that concordance for anencephaly or spina bifida is less frequent in twins of unlike sex. Twins concordant for these malformations tend to be aborted in early pregnancy, but high abortion rate fails to account for the discrepancies between monozygous and dizygous twins. There is no apparent reason why concordant dizygous twins should be aborted, and monozygous twins spared. From these observations, Rogers (1976) hypothesized as follows: Monozygous twins with defects of neuroepithelial closure are liable to fuse to each other with the production of "double monsters." Twins, regardless of zygosity, are liable to adhere to the amniotic membrane at the site of the epithelial defect. When dizygous twins are separated by an amniotic partition, this dividing septum may break down due to adherence of one twin to the partition. Once this event occurred, dizygous twins would find themselves in a secondarily monoamniotic cavity, and would be apt to fuse, and undergo a fetus-fetus interaction that leads to partial or complete destruction of one twin. "The partially destroyed twin may still be recognized in the survivor as a patch of inappropriate skin (scalp?) covering the defect, or as a teratoma." (Rogers, 1976.)

Whereas this hypothesis necessitates a number of ill-defined processes to sustain its credibility, it is nonetheless appropriate to attempt, as Rogers (1976) points out, systematic verification of the testable predictions that ensue, namely: "that the incidence of intraspinal and pineal teratoma may vary in time and place with spina bifida and anencephalus, and that the scalp type hair found over and around spina bifida lesions may, in male infants, carry female chromosomes."

"Fetus-in-fetu"

Whatever the merits of a hypothetic fetus-fetus interaction as an explanation of the origin of teratomas, the existence of "included fetuses," though rare, is generally accepted. The term "fetus-in-fetu" is reserved for those formations in which "fetiformity" is carried to a very high degree, and in which there is evidence of axialization and metameric segmentation. Regardless of the prevailing uncertainties about the exact pathogenesis of this condition, there is agreement on the main features that allow its diagnosis, and on some practical principles of its treatment.

"Fetus-in-fetu" occurs predominantly in the upper retroperitoneum (Grosfeld et al.; Gross and Clatworthy), less frequently in the pelvis (Numanoglu et al.), ileal mesentery (Lee), and other intra-abdominal sites (Lord). More than one included fetus have been described in the same patient (Gross and Clatworthy). Unlikely sites of occurrence, such as the cranial cavity (Kimmel et al.), are on record; there is doubt, however, as to whether cases reported outside the pelvis, abdomen, or retroperitoneal space have been correctly classified. Usually, this condition presents as a palpable intra-abdominal mass, or a rapidly enlarging abdomen under pressure. Symptoms of gastrointestinal obstruction may predominate. The single most important diagnostic procedure for its detection has been the plain abdominal radiograph (Gross and Clatworthy; fig. 5). Due to the rarity of this lesion, however, the roentgenologic diagnosis is often made in retrospect, after the mass has been excised (pl. I-B; fig. 6). Of 18 cases reviewed and tabulated by Knox and Webb, the diagnosis was made in the infantile period in all but two patients, 8 and 10 years old, respectively. If the mass is not excised, it is capable of growing. Growth seems to depend on the state of vascularization of the "included fetus." The treatment of choice is surgical removal of the "fetus." Delay in operation carries the risk of complications,

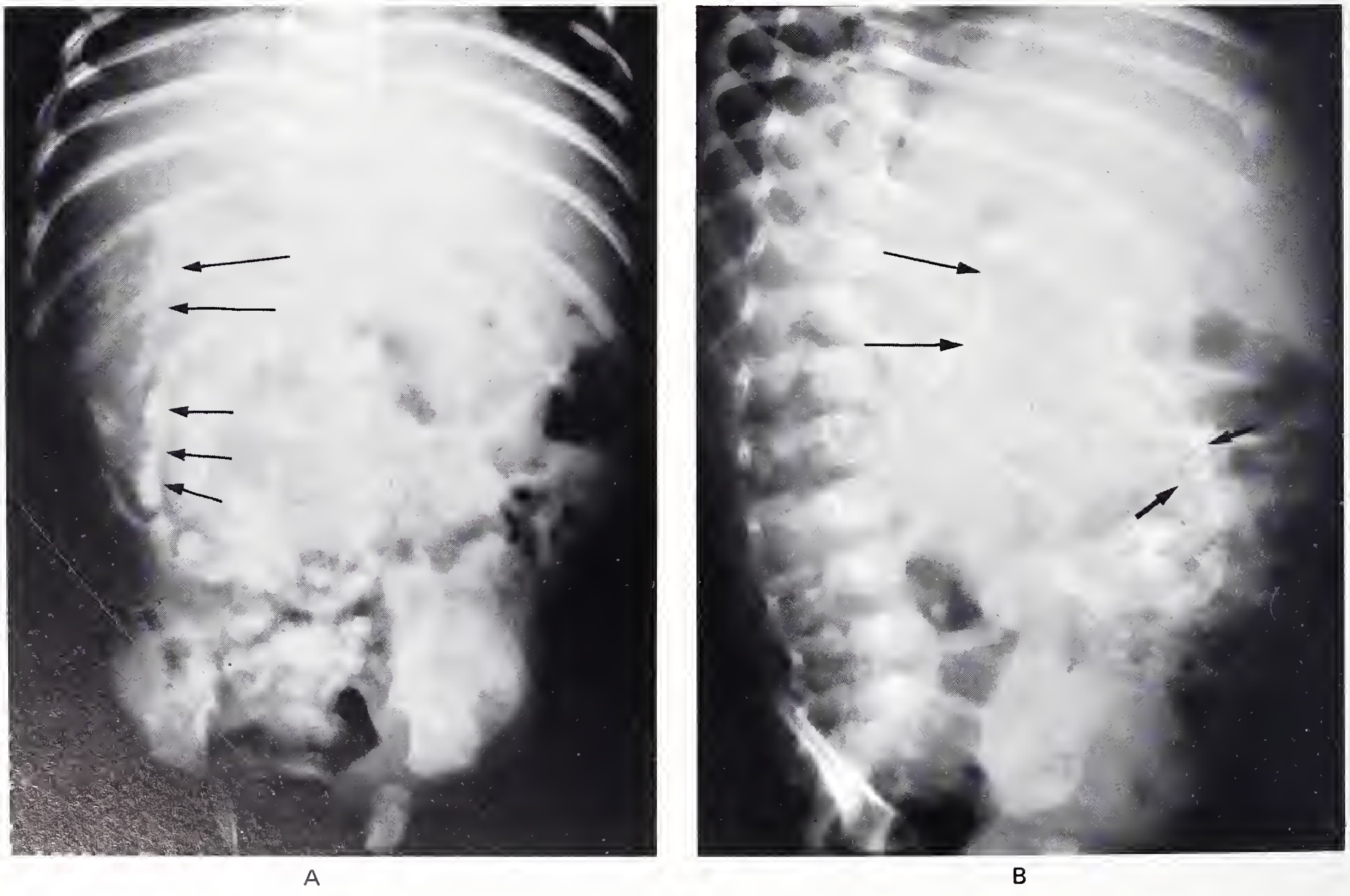
A
B

Figure 5
(Figures 5, 6, and plate I-B from same case)
FETUS-IN-FETU
Plain x-ray film of the abdomen of a 6 week old male child shows well organized bony fetal parts in the retroperitoneum (long arrows mark fetal long bones; short arrows mark spine). At operation, a fetus-in-fetu was found in contact with the undersurface of the liver, displacing the right kidney anteromedially. (A) Anteroposterior view; (B) lateral view.

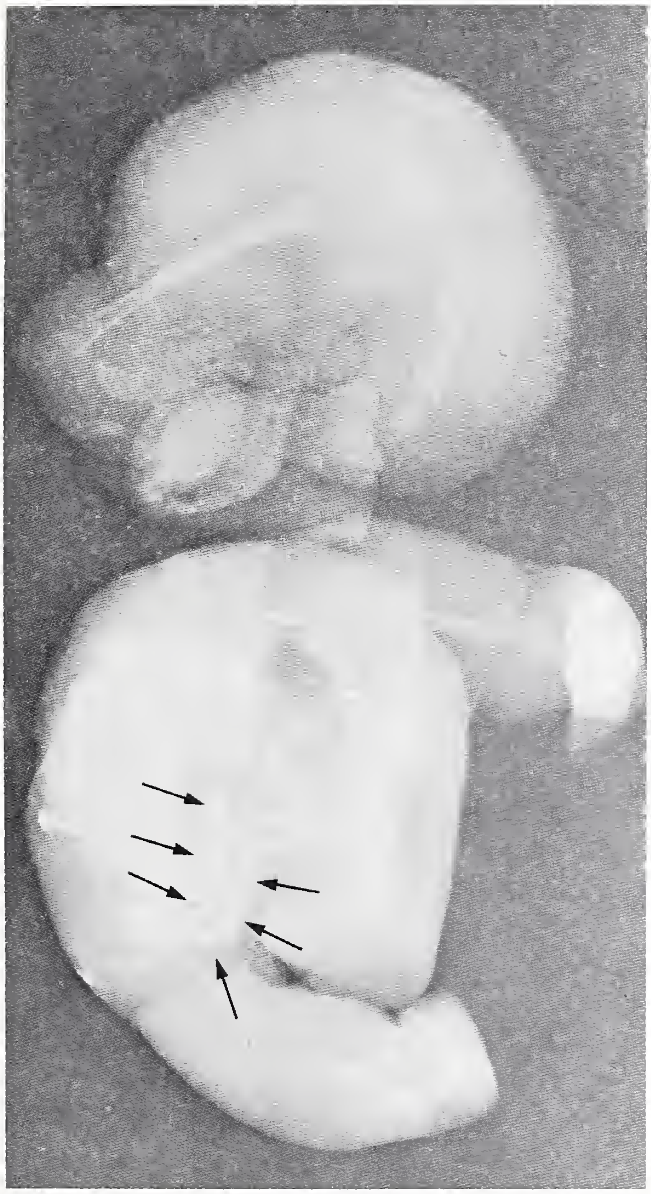

Figure 6
FETUS-IN-FETU
Dilute barium was injected through what was interpreted as a patent omphalomesenteric duct of the excised mass, thus revealing primitive intestinal loops (arrows). (From Grosfeld, J.L., Stepitar, D.S., Nance, W.E., and Palmer, C.G. Fetus-in-fetu: an unusual cause for abdominal mass in infancy. Ann. Surg. 180:80-84, 1974.)

among which bleeding and gastrointestinal obstruction are the best known. The "fetus" is surrounded by a fibrous membrane grossly reminiscent of the fetal membranes in normal placentation. A cordlike structure may join the fetus to the enclosing capsule. In a personally studied example, reported by Grosfeld and associates, the "capsule" was formed by a fibrous tissue wall lined by thin polystratified, keratin-producing epithelium. There was no resemblance to amniotic epithelium or any similarity to the fibrous tissue layers of the amnion. Likewise, there was no evidence of chorion. Villus-like tissue, allegedly representing chorionic villi, has been reported (Lee), but the illustrations are not entirely convincing of the trophoblastic nature of such structures. Chorionic gonadotropins have not been investigated in cases of "fetus-in-fetu." Gross and Clatworthy suggested that there may be a risk of malignant transformation when the enclosing capsule is totally or partly left behind, as it sometimes is, due to technical difficulties of the surgical procedure. This hypothetic risk has never been documented.

In summary, certain tissue growths possess such a striking "fetiform" quality that they look, indeed, like deformed individuals. In contrast to the chaotic aggregation of tissue structures found in most teratomas, "fetus-in-fetu" simultaneously exhibits several organ systems, and in no case is only part of a fetus present, such as caudal area or limbs alone (Lord). Furthermore, a vertebral axis may be found, and ribs or other evidence of metameric segmentation can be seen. These lesions are currently named "fetus-in-fetu," and interpreted as "included twins." Since the etiopathogenesis of human teratomas is incompletely understood, no definitive generalizations seem warranted about the nature of these lesions, or as to how they relate to teratomas. At present, attribution of the name "fetus-in-fetu" conveys the idea of high organotypic development and presence of a vertebral axis, with arrangement of tissues around this axis. The mass of tissue is enclosed by a capsule and suspended by a peduncle in the manner of an umbilical cord. All these structural features notwithstanding, the existence of borderline cases of difficult classification is acknowledged (Ashley). Obviously, the mere presence of a vertebral or notochordal axis is a highly arbitrary criterion, and more refined studies will have to be performed before this question is settled. Grosfeld and associates took the position that "fetus-in-fetu" represents the inclusion of a monozygotic twin, and is embryologically and anatomically different from a teratoma. The evidence they adduced was based on the findings of cytogenetic studies performed on a retroperitoneal mass discovered in a 4 month male infant, and interpreted as "fetus-in-fetu." Both "subjects," the mass and its host, had a 46 XY karyotype; both showed heteromorphic fluorescent markers in chromosomes #3 and #21; cultured fibroblasts from both demonstrated the same antigens in two subloci. Sufficient blood could not be obtained for genotyping, but the identity of histocompatibility types and the chromosomal banding studies were deemed sufficient to conclude that monozygosity and "inclusion" of a twin accounted for the presence of the retroperitoneal mass. The same conclusion was reached by Boyce and co-workers after serotyping studies. However, the very rare occurrence of this condition has precluded further studies of this kind, and it remains debatable whether the available evidence is, in fact, conclusive. The identity of included fetuses and teratomas has been strongly denied, but Potter and Craig continue to acknowledge that an "even progression" may be seen between normal twins, conjoined twins, parasitic twins, enclosed fetuses, and teratomas.

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PROPERTIES AND BEHAVIOR OF TERATOMAS IN VITRO

Experimental teratoma cells are of unique value as a model system for studies of cell differentiation and tumor formation. Much of the work using this model has been recently reviewed (Martin), but advances in this field take place at such a rapid pace that reviews become grossly incomplete or obsolete almost as soon as they are prepared. Only some of the in vitro characteristics of teratocarcinoma cells will be covered in this section. Largely, experimental work on teratoma cells is based on the murine teratocarcinoma model. Unless otherwise specified, this system is referred to in the following discussion.

Cultured Cells

The embryonal carcinoma cells are, as was noted precedingly, the malignant cells. Only that part of a teratoma which contains these cells will be retransplantable. It has now been shown that, when grown in tissue culture, these cells retain the capacity to give rise to a variety of differentiated tissues, i.e., they remain pluripotent under the conditions of tissue culture. This is true for embryonal carcinoma cells of spontaneously occurring teratocarcinomas (Finch and Ephrussi; Kahan and Ephrussi), as well as for embryo derived teratocarcinomas (Martin and Evans). The pluripotency of these cells is demonstrated by injection into an appropriate recipient. A single cell is capable of originating a tumor (Kleinsmith and Pierce), although teratocarcinoma formation usually requires 2 x 10^4 cells (Jakob et al.); ten cells are enough to produce a tumor in "immunologically privileged" sites, such as testis and eye. Growth in the recipient will demonstrate the cells' capacity for multifarious tissue differentiation. Embryonal carcinoma cells have been used in "reconstitution" experiments, in which cells from different lines are introduced in the blastocele of normal mouse blastocysts. As discussed before, many of these "grafted blastocysts" have produced chimeric mice. Embryonal carcinoma cells in culture grow in small colonies, but depend for homogeneous growth on passages on "feeder" cell layers (Kahan and Ephrussi; Martin and Evans), usually mitomycin treated fibroblasts. In the absence of "feeder" cells, the embryonal carcinoma cells form clones containing fibroblast-like cells of uncertain derivation. Feeder independent cell lines have also been obtained (Jakob et al.).

The karyotype of mouse teratocarcinoma cells is often abnormal (Martin), but pluripotent embryonal carcinoma cells grown in culture remain euploid with remarkable consistency (Guénet et al.), probably as a result of their similarity to, or identity with, normal embryonic cells.

Teratocarcinoma cells and mouse fibroblasts have been hybridized experimentally; the multipotentiality of the teratocarcinoma cells is thereby limited in its range of expression (Jami and Ritz).

Immunologic Properties

A critical review of research on the cell surface antigens of murine teratocarcinoma cells was prepared by Gachelin. Several cell lines have been grown from teratocarcinomas and used for the production of antisera. F9 is one such line, known as "nullipotent" because it produces embryonal carcinoma cells (ECC) in vitro, with almost no evidence of differentiation; in vivo, it gives rise to tumors containing exclusively ECC. After suitable absorptions (on Pys-2 cells, in the case of F9), the antisera are used for detection of well defined surface antigens present on embryonal carcinoma cells. A remarkable finding of this research has been that certain antigens, such as F9, C, and PCC4, are seen only in cells that can be defined as ECC. Neither primitive cells from tumors other than teratoma, nor virus-transformed cells ever express these surface antigens. With rare exceptions, embryonal carcinoma antigens are common only to embryonal carcinoma cells and to cells of the normal embryo. Thus, they are oncofetal antigens.

As expected, ECC share antigenic properties in common with normal embryo cells. Major histocompatibility H-2 antigens of adult mice are absent from both embryo cells and ECC (Artzt et al.; Artzt and Jacob). This is striking, as nearly all cell types of the adult and many tumor lines express H-2 antigens. The embryonic membrane antigen F9 has been found in several lines of murine ECC mouse embryos and sperm, but not in adult cells. This selectivity of occurrence suggests that the F9 antigen may play an important role in development, although the nature of this role remains unknown. Mouse ECC or embryonic cells that express F9 antigen lack H-2 antigens. F9 is shared by humans and mouse ECC in culture (Holden et al.). This antigen evokes an "autoantibody" response in syngeneic systems. Accordingly, the possibility exists to develop a clinically applicable immunologic test for the detection of these antibodies in patients with teratomas containing ECC. Since human teratoma cells have been found to share other antigens with mouse teratoma cells (Ostrand-Rosenberg et al.), there is a very real promise for the future development of immunologic technics of clinical value in diagnosis and therapy. This is merely an example of the possible ramifications of work tending to uncover the presence of specific, highly sensitive markers of cancer cells; it illustrates the relevance of the murine model to human cancer, as shown by the sharing of identical biologic characteristics. Work with antibodies raised against ECC lines indicates that antigens shared with normal embryo cells are lost from the differentiated tissues that stem from ECC (Gooding and Edidin).

The T-locus is a cluster of genes located on the 17th chromosome. Presumably, it contains the genes that specify the surface antigens of sperm (Yanagisawa et al.). It is believed that the major antigen on ECC is dictated by the wild allele of the t^{12} gene (+12). Present evidence tends to define controlling genes crucial to embryogenesis at the T-locus complex (Gluecksohn-Waelsch and Erickson). Thus, it is hypothesized that each stage of embryogenesis is triggered by the appearance of genetically controlled cell-surface components that have a special effect on morphogenesis. The cell-surface antigens could act as recognition sites. In this manner, the t^{12} mutants affect the formation of blastocyst, the t^{o} mutations affect the cleavage of the inner cell mass, and so forth. Of central interest to the cytogenetic theories of origin of teratomas is the sharing of common antigens by murine ECC, early embryo cells, and, as indicated above, human ECC. The time of appearance of these antigens, their time of disappearance (in the course of differentiation) and substitution by newly emergent ones, and the mechanism whereby antigenic components are formed and lost are problems that currently occupy the attention of researchers (see review by Gachelin). New knowledge of these biologic phenomena is expected to throw light on heretofore elusive mechanisms of cell differentiation.

Embryoid Bodies

Small structures that morphologically resemble early human embryos are known to occur in teratomas since Peyron described these formations in testicular lesions. Peyron believed that these structures, known as "embryoid bodies" (EBs), were entirely homologous to a normal embryo; he undertook an extensive analysis of tumors containing EBs, and set down the basis on which later ideas attributing a parthenogenetic origin to germ cell tumors were contructed. The structure of EBs in human teratomas has been well illustrated (Evans), and the observations support the interpretation that EBs are comparable to normal embryos of one to two weeks' gestation. Occasionally, a tumor will be found entirely composed of EBs, and deserving the name of "polyembryoma"; more often EBs coexist with better differentiated tissues. The pathology literature dealing with EBs in human teratomas has been reviewed several times (Marin-Padilla; Stevens).

In the mouse, EBs were first observed by Stevens in a retroperitoneal metastasis of a testicular teratoma. Pierce and collaborators then found that when partly necrotic areas of solid teratomas sloughed into the ascitic fluid, EBs were formed. Thus, it was established that teratocarcinoma of the mouse, in its ascitic form of growth, constitutes a ready source of supply of myriads of EBs for experimental studies. Structurally, the EBs thus obtained are either "simple" or "cystic" (Martin; Martin et al.; figs. 7, 8). "Simple" EBs are solid rounded aggregates of cells. The external layer of cells is endodermal, and the inner core consists of embryonal carcinoma cells. These component cells can be distinguished ultrastructurally (Teresky et al.): the outer, or endodermal cells, have abundant rough endoplasmic reticulum and synthesize basement membrane products; the inner mass of cells have many free ribosomes and are poor in organelles. It should be noted that in the 5 day old mouse embryo, the external layer of cells is endodermal in nature. Accordingly, EBs are comparable to a conceptus of this age rather than to the blastocyst (3.5 days), in which the external layer is trophoblastic in nature; EBs do not contain trophoblastic elements (Martin; Martin and Evans; Martin et al.).

"Cystic" EBs are apparently derived from "simple" EBs (Pierce et al.), and thus show a more complex structure. To some extent, although with some differences, the formation of "cystic" EBs parallels normal embryonic development; "cystic" EBs may be obtained from "simple" EBs removed from the peritoneal cavity and maintained in vitro (Holden et al.; figs. 7, 8). Martin and associates have made a detailed analysis of the morphologic changes that occur in the process of transformation of "simple" into "cystic" EBs. This process is one of synchronous differentiation in which the entire cell population participates. Martin and his co-workers noted that the pattern of development closely resembles that in normal mouse embryogenesis up to the time of formation of the third germ layer,

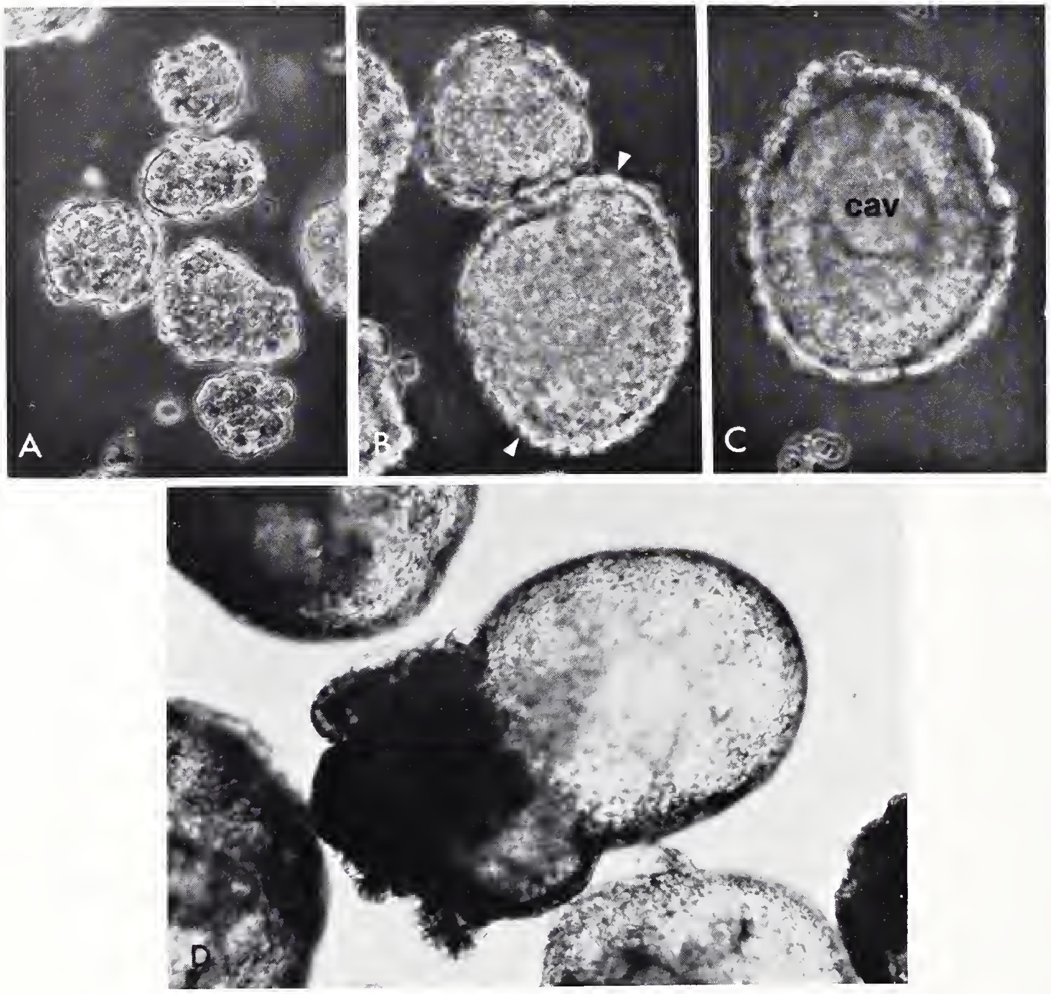

Figure 7
TERATOMAS IN VITRO
Embryoid bodies as observed in the phase-contrast microscope. (A) Embryonal carcinoma cells just detached from the tissue culture substratum. (B) After two days in suspension, with outer layer of endoderm (pointers). (C) Cavitation. X200. (D) Cyst formation after 10 days in culture. X90. (Courtesy of Dr. G. R. Martin. From Martin, G.R., Wiley, L.M., and Damjanov, I. The development of cystic embryoid bodies in vitro from clonal teratocarcinoma stem cells. Dev. Biol. 61:230-244, 1977.)

the mesoderm. At this point, some EBs proceed to form mesoderm in a relatively normal way by proliferation of cells that constitute a third layer, whereas in most, the mesoderm arose by an anomalous mechanism that was difficult to define. One possibility suggested was that mesoderm in "cystic" EBs forms by differentiation in situ of attenuated ectoderm. One of the most important advantages of EBs for studies of cell differentiation and determination is that the differentiative capacity of a teratocarcinoma remains similar, whether it is maintained as a solid tumor or in the form of EBs (Iles). Whereas the solid growths usually contain a wide variety of differentiated tissues with interspersed nests of embryonal carcinoma cells, the latter cells form a large proportion of the EBs. The isolation of clonal embryonal carcinoma cells is thus facilitated from work with EBs. Various embryonal carcinoma cell lines have been isolated in this manner, and some of their cultural characteristics investigated (Jakob et al.; Kleinsmith and Pierce). Furthermore, EBs are useful in studying early embryogenetic events, since they furnish a large population of cells in which these early events (for instance, endodermal formation) occur, and since such biologic phenomena are entirely comparable to those of the normal embryo. The obvious course that future research will take will be the application of a number of biochemical and immunologic technics for study of cell differentiation in EBs.

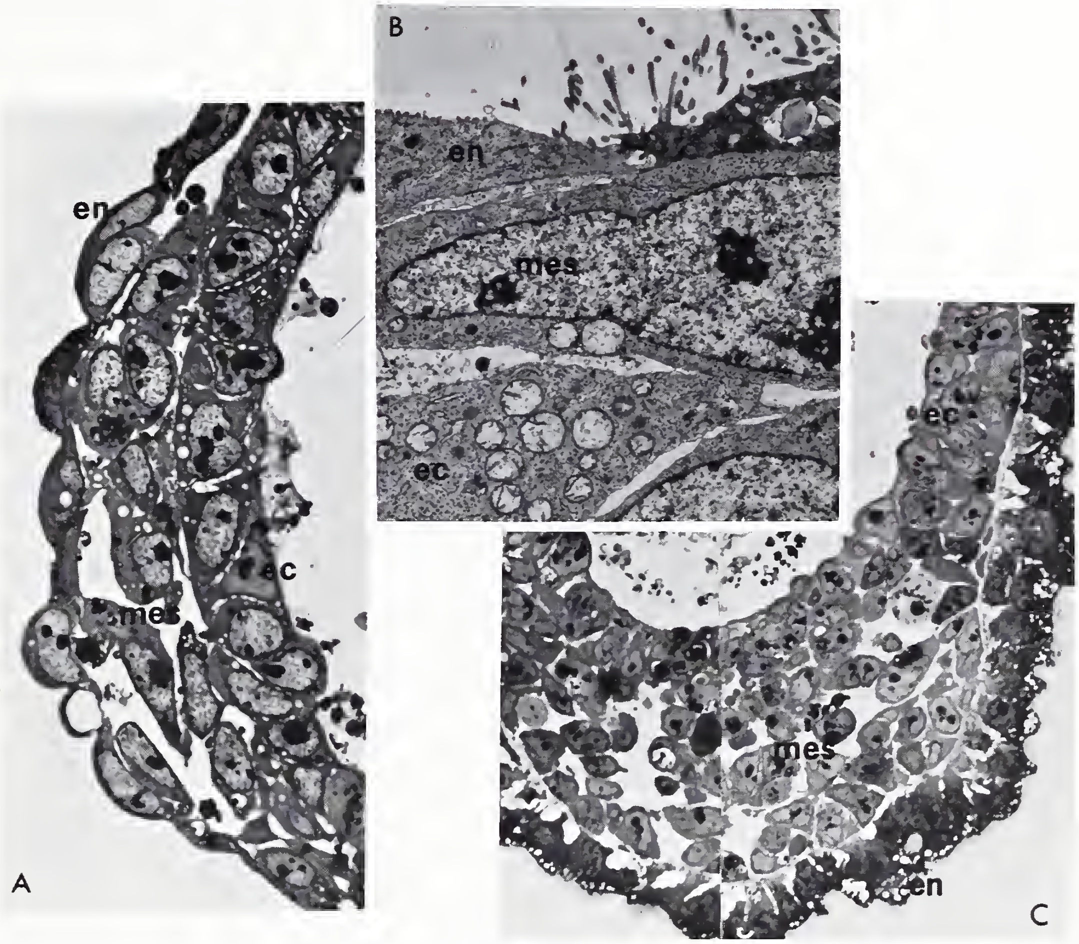

Figure 8 (A, B, C)
TERATOMAS IN VITRO
Mesoderm formation in embryoid bodies. (A) Migration of mesodermal cells (mes) between ectoderm (ec) and endoderm (en). X400. (B) Ultrastructural detail, showing microvilli in external endodermal layer. X5941. (C) A primitive streaklike area. X400. (Courtesy of Dr. G. R. Martin. From Martin, G. R., Wiley, L. M. and Damjanov, I. The development of cystic embryoid bodies in vitro from clonal teratocarcinoma stem cells. Dev. Biol. 61:230-244, 1977.)

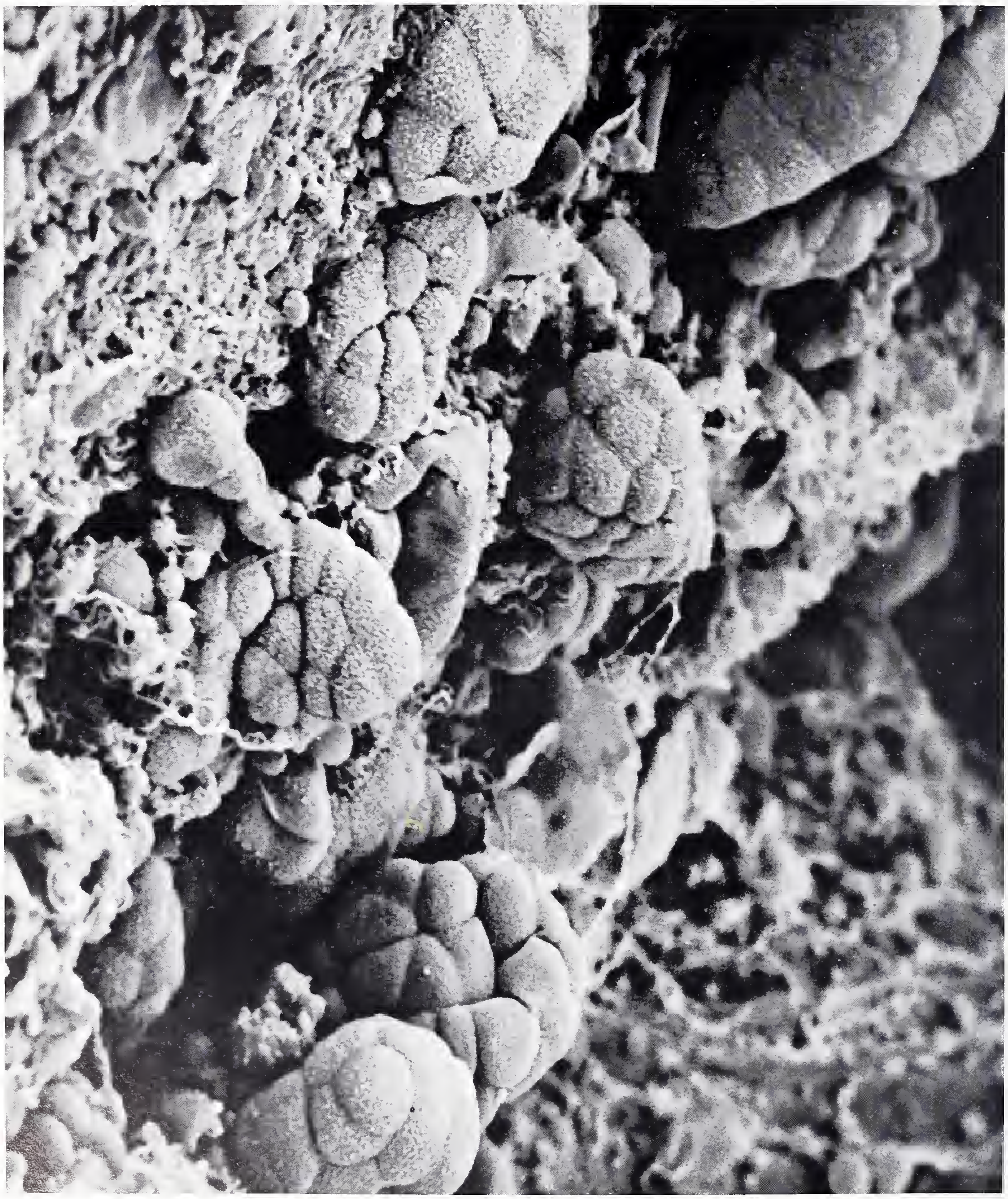

Figure 8 (D)
TERATOMAS IN VITRO
Embryoid bodies in the peritoneal cavity, as revealed by the scanning electron microscope. X680. (Courtesy of Dr. J. Gaillard, Pasteur Institute, Paris, France.)

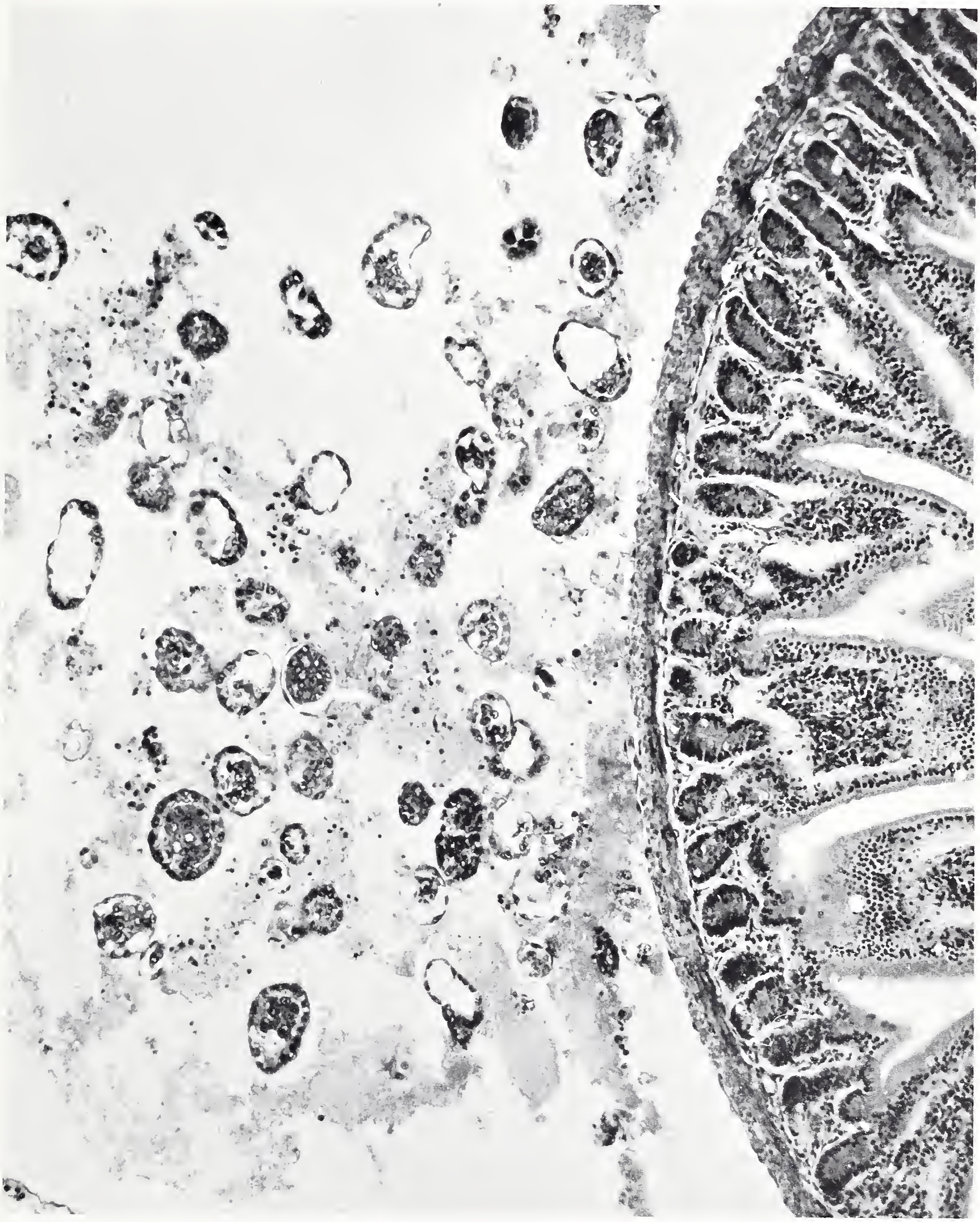

Figure 8 (E)
TERATOMAS IN VITRO
Histologic section showing embryoid bodies growing in the peritoneal cavity of a 129/sv mouse, 14 days after implantation of embryonal carcinoma cells. X60. (Courtesy of Dr. J. Gaillard, Pasteur Institute, Paris, France.)

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CONSIDERATIONS ON PATHOGENESIS

Certain facts of the natural history of human teratomas seem so consistent that room must be made to accommodate them in theoretical schemes that purport to explain the origin of these tumors. Among the questions that need to be answered are the following: Why should gonadal teratomas be more common than extragenital ones? Why more in the ovary than in the testicle? Why do ovarian teratomas appear overwhelmingly as the benign "dermoid cyst" type, whereas testicular teratomas often are malignant? Why do testicular and extragenital teratomas in very young children tend to behave as benign tumors, whereas testicular teratomas of adults are very often malignant? And why is it that the reverse obtains in ovarian teratomas? Whereas a definite answer to these questions is not available, some speculations based on objective data bearing on these questions are summarized below.

Assuming the validity of the germ cell theory of origin, the different clinical significance of ovarian and testicular teratomas forces a reconsideration of possible differences in primary sex cells. One major difference is the large amount of cytoplasm present in the ovum, as contrasted with the male gamete. It has been speculated that the factors activating the nucleus of the fertilized ovum reside in the cytoplasm of the oocyte, and are produced by genetic activity during ripening of the follicle. In further elaboration, Crockford and associates state: "If it is assumed that the nuclear activators are no longer synthesized in the fertilized ovum and are . . . particulate . . . , as successive cell divisions occur, the number of particles per cell will diminish with each division. In the absence of a regulating mechanism, . . . there will be a probability that some cells will contain more particles than others, and a small probability that one or two cells will contain many more. At the stage of germ cell migration these cells are not very numerous and may well be less generations away from the fertilized ovum than other body cells. In this array of supposition, there exists the possibility that a germ cell in the testis, or ovary, may contain enough nuclear activators to be totipotent when the cells around it are settling down to produce a differentiated gonad."

Clearly, the hypothesis that proposes the existence of a particulate material in germ cells, residing in the cytoplasm, and acting upon nuclear function to effect a certain determining influence, is the old theory of the "germ plasm." This theory, in its original form, suggested the continuity of the germ cell line from one generation to the next. It maintained that not all the progeny of a fertilized gametocyte is used to form the body, but that some cells remain unchanged, and pass on as reproductive elements to succeeding generations. A somewhat modified version, attributed to Weismann (1892) proposed that a substance called "germ plasm," rather than entire cells, was handed down from parent germ cells to the germ cells of the offspring. Hereditary tendencies were believed to be transmitted thus from one generation to the next, eternally unchanged: the transmission of "germ plasm" from the fertilized ovum to the newly formed gonad was believed by Weismann to be carried out by a definite series of cells, the *Keimbahn* or germ track (germ cell line). Although this old theory has undergone alternating periods of popularity and neglect, contemporary investigations have not wholly superseded its central premise. As recently reviewed by Eddy, there is ultrastructural and experimental evidence suggesting that "germinal plasm" may exist in cells during development in a number of species. The evidence is still circumstantial. Germ cells often contain an ultrastructurally visible, electron-dense substance called "nuage," but it has yet to be shown that this substance is able to exert a determining influence on the germ cell line.

Erickson and Gondos have called attention to several aspects of the biology of germ cells which may be important in explaining the different behavior of ovarian and testicular teratomas. In the fetal ovary, germ cells (oogonia) replicate extensively by mitosis, so that approximately 600,000 are present at the second month of gestation, and one million at birth. A small proportion initiate meiosis early in fetal development. By midgestation, meiosis reaches a "resting" phase in many oocytes, but then meiosis is "arrested" for years, to resume at puberty. In contrast, meiosis does not take place at all in the fetal testis; meiotic replication in male sex cells begins only at puberty. Thus, a temporal association seems to exist between malignancy of gonadal teratomas and peak periods of meiotic activity of germ cells. Malignant teratomas of the testes appear most frequently 5 to 15 years after the initiation of spermatogenesis; malignant teratomas of the ovary have their peak frequency 5 to 15 years after the period of maximal replicating activity.

A second difference in gametogenesis is the number of cellular interconnections. In the male, a large number of cell-to-cell bridges develop during spermatogenesis, which are thought to play a role in the normal synchronization of this process. In the ovary, germ cell interconnections are more limited, and restricted to the fetal period of development. Hence, Erickson and Gondos point out that the time of appearance of malignant teratomas in the gonads of each sex is temporally related — assuming a constant lag period — with the time of maximal intercellular connections.

A third difference refers to the obvious chromosomal disparity in male and female cells. That the Y chromosome may exert an influence in gonadal tumor malignancy is suggested by the greater incidence of extragonadal teratomas in girls. In patients with gonadal dysgenesis, germ cell tumors develop almost exclusively in individuals with a Y chromosomal complement. Ovarian teratomas are believed to arise from parthenogenetic self-fertilization of germ cells (Hecht et al.; Linder et al.). It thus appears of particular relevance to study the mechanisms that trigger parthenogenesis in different animal species, and to account for its comparatively lower success in mammals. This problem is bound to the elucidation of the nature of the contribution of sperm to the zygote. Other than a haploid set of chromosomes, the male cell furnishes to the fertilized egg largely unknown attributes that direct the zygote to the successive divisions that start the formation of a new individual. Better knowledge of these properties will be conducive to greater understanding of the pathogenesis of teratomas.

Working on Linder and associates' pathogenetic scheme, Riley and Sutton propose that a genetic mutation occurs in the progenitor gonadal cells (oogonia or spermatogonia), and that this mutation may explain the different clinical behavior of ovarian and testicular teratomas. The hypothesis assumes that a growth-controlling locus is deleted by a mutagenic event. The mutation would occur in one of a pair of homologous chromosomes of spermatogonia. As the chromatids are replicated during meiosis I, there would be production of primary spermatocytes homozygous (—/—) for the mutation. In turn, these would generate secondary spermatocytes homozygous for the mutation, and be capable of giving rise to the diverse tissues that compose a teratoma. In contrast, if the mutation were to occur in one chromatid (not an entire chromosome) of a primary oocyte, the result would be, at the first meiotic division, the production of a secondary oocyte heterozygous for the mutation (+/—). Since the assumption is that the mutation confers malignancy, the phenotypic expression of the heterozygous state would be abnormal proliferation, but not complete breakdown of tissue homeostasis (i.e., a benign tumor), whereas the homozygous state, lacking complementation, would be expressed as a malignant neoplasm. This hypothesis indicates that primary oocytes are at greater risk of mutation because they are "arrested" or "stored" during early meiosis. However, since the "storage" or "arrest" (dictyotene stage) takes place after DNA replication, when the cell already has four chromatids, the consequence of a mutation at any locus is that the secondary oocyte will be heterozygous for the mutation. Thus, the hypothesis accounts for the greater number of ovarian versus testicular teratomas, and the higher frequency of benign cases among the former, and of malignancy among the latter.

Among the predictions of this hypothesis, Riley and Sutton cite the occurrence of teratomas in which the mutation affects the oogonia before the beginning of meiosis in the fetus: such tumors are expected to be malignant, and a proportion of these should arise in extragonadal sites. Conversely, testicular teratomas may be benign if the mutation-bearing chromosomal segment is exchanged during meiotic "crossing-over." Furthermore, the existence of seminomas within teratomas would be explained not as a fortuitous association, but as a genetically correlated event. A second mutation on primary spermatocytes might produce cells incapable of undergoing differentiation (seminoma cells). As Riley and Sutton remark, it is difficult to devise a way of testing the hypothesis. Its value resides in a coherent proposal of the effect of mutations at different stages of gametogenesis. The quoted authors also state that in species in which oogenesis is delayed, the proportion of malignant ovarian teratomas should be found greater. This hypothesis has yet to be investigated.

Based on the occurrence of hereditary tumors, bilateral teratomas, and pedigrees of families with inordinately high frequency of teratomas, Hecht and collaborators suggested that there may be genes which control the formation and fate of the second polar body, and that a mutation of these genes might account for disturbances in this process. This would explain a familiar predisposition for teratomas in certain families. Instead of the influence of an inherited gene, Riley and Sutton propose a random error in meiosis, as detailed above. In their view, the extreme rarity of bilateral teratomas compared to the number of maturing oocytes, and the variable expression in the predisposition to develop these tumors, indicates that a degree of randomness exists in the pathogenesis of these tumors.

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Cytogenetic Data

Germ cells, the presumptive cells of origin of teratomas, in addition to undergoing mitotic division, also divide by *meiosis*. This is in contrast to somatic cells which only divide by mitosis. A brief account of the process of meiosis seems necessary to provide a better background to the work of some investigators on the origin of teratomas (fig. 9).

Before ova or sperm are formed, primitive gonadal cells (oogonia or spermatogonia) are mitotically active and have 46 chromosomes. At the start of meiosis (zygotene stage) these chromosomes lie together in homologous pairs. Each of the chromosomes then builds a replica of itself, so as to produce two equal pieces, called chromatids, joined together at the centromere (pachytene stage). The next step is most important. Pieces of broken chromatids cross over and realign (diplotene stage), thus exchanging genetic material from one chromosome to the next. The resulting "mixed" chromosomes align themselves along the line of fission of the gonadal cell. The filaments of the spindle apparatus attach themselves to the centromere of the chromosomes and contract, thereby pulling each member of the pair into the respective poles that will become the daughter cells. This way, each resulting cell has half the number of chromosomes that was present in the gonadal cell. This completes the "first meiotic division." In the testis, each of the two cells goes on to the "second meiotic division." In the ovary, only one cell is viable, the other becomes the first polar body, which is lost. The 23 chromosomes line up again, each producing two chromatids, along the cell's equator, to begin the "second meiotic division." Now an important change takes place: each centromere replicates and becomes split longitudinally, so that each chromatid has its own centromere. When the filaments of the spindle apparatus attach to the centromeres and contract again, each chromatid (now considered a chromosome in its own right by virtue of having its own centromere) will be pulled into the respective daughter cell. Thus, at the end of the "second meiotic division," four gametes will have been produced from each gonadal cell. This applies only to the testis. In the ovary, only two cells are produced, because the "second meiotic division" produces, as did the first, one viable cell and one polar body.

Each resulting cell has only half the number of chromosomes, or haploid number, of the parent cell. In the normal human ovary, at the time of birth, germ cells are partly engaged in the "first meiotic division" (meiosis I). The process of meiosis is suspended during prophase, in a modified diplotene stage, or *dictyotene*. Crossing over has taken place, but each homologous member of the 23 chromosome pairs is not pulled to the corresponding daughter cell for a long time. Years later, when the host reaches puberty, meiosis I will be completed. The process is

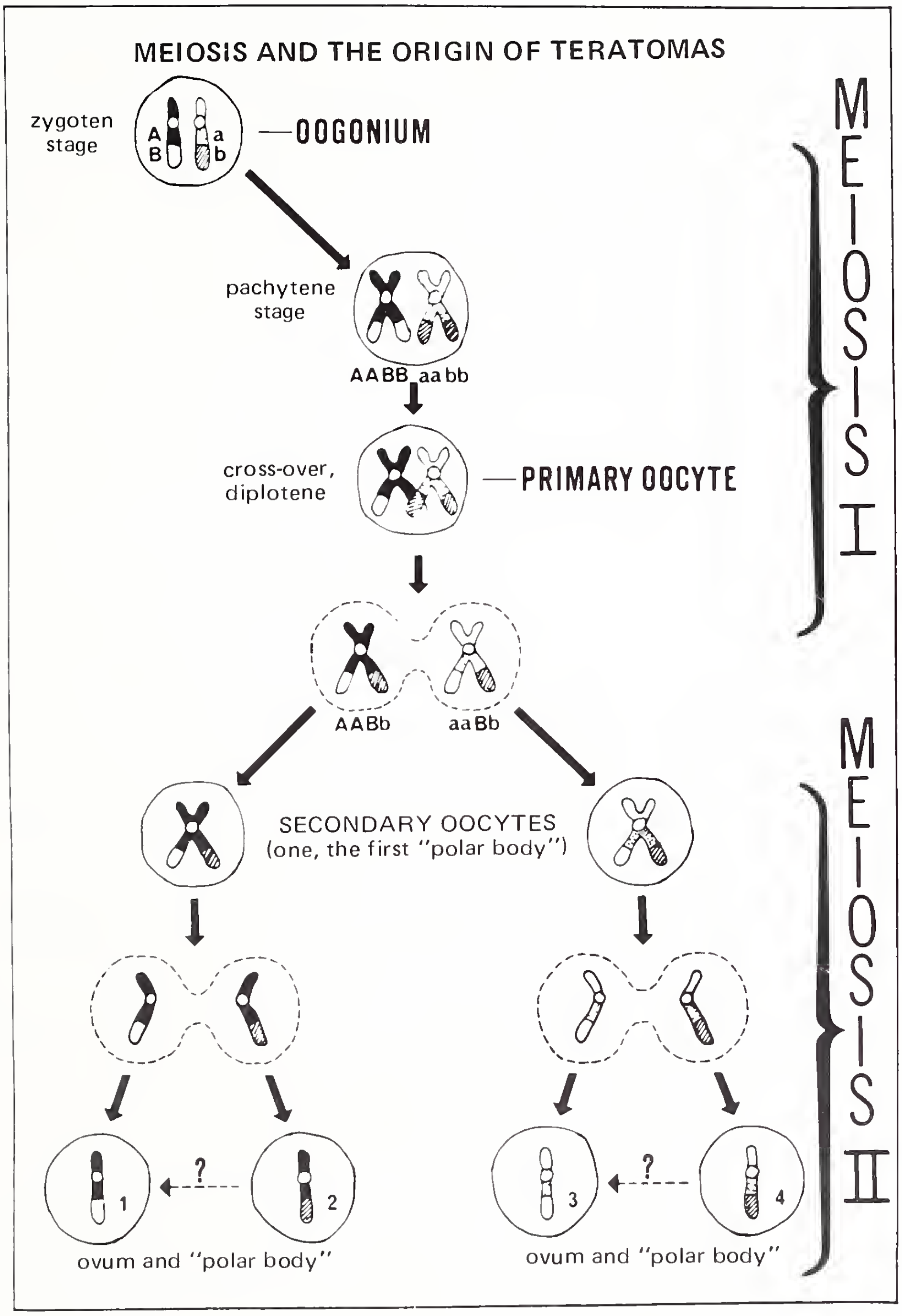

Figure 9
CYTOGENETIC DATA

For simplicity, only one pair of chromosomes is represented. The centromere is shown as an open circle, and genetic polymorphisms as black (**A**), white (**B**), dotted (a), or hatched (**b**) areas of the corresponding chromatid. Crossing-over apparently does not occur close to the centromere (**A** and a regions); the host and oogonium are homozygous at this region. Linder and associates found that teratoma cells are diploid cells which express homozygosity at some gene loci (close to the centromere) and heterozygosity at other loci; they are either **AABb** or **aaBb**. This is the condition of secondary oocytes after one crossing-over event. Accordingly, the hypothesis proposes that the progenitor cells of teratomas go through meiosis I, but become arrested at meiosis II, so that the replicated centromeres separate, but remain within a single nucleus. The same result would be accomplished if the second polar body were to fuse with the ovum; this possibility is indicated in the diagram by a dotted arrow with a question mark. The hypothesis does not distinguish between suppression of meiosis and fusion of the ovum with the second polar body.

hormonally activated just before ovulation. Meiosis II does not take place at all, unless fertilization has occurred.

Linder and associates studied a series of benign cystic ovarian teratomas and normal host tissues. All had 46,XX (diploid) karyotype. These researchers then compared morphologic chromosome markers and electrophoretic variants of different enzymes (genetically controlled at specific loci) in normal tissues of the host, and in teratoma cells. They found that the normal tissues were heterozygous for many chromosomal polymorphisms near the centromere, whereas the teratomas were uniformly homozygous. In regard to the enzyme variants, the host tissues were uniformly homozygous, whereas the teratomas were either homozygous or heterozygous at one or more enzyme loci. There were no phenotypes in the tumor that were absent in the host. Linder and associates, with these findings, reasoned as follows:

Firstly, teratomas cannot arise from germ cells in which meiosis I does not take place. If this were the case, chromosomal and genetic markers for which the host is heterozygous would also be usually heterozygous in the tumor. This was not found. Secondly, teratomas could arise from a mature gamete that, after going through the first and second meiotic divisions, would double the number of its chromosomes and proliferate to form a teratoma. The tumors would then be expected to be homozygous for all chromosomes *and* gene markers, but this was not observed. Thirdly, two mature gametes, formed independently, could fuse together (autofertilization) and form a diploid cell, which in turn would proliferate and give rise to a teratoma. One would expect, if this situation obtained, to find equal numbers of homozygous and heterozygous tumors (1:2:1 distribution, as obtained from all possible combinations of gametes labeled 1, 2, 3, and 4 in figure 9), but the findings did not support the expectation. This left only two possibilities to account for the origin of teratomas: either the second meiotic division does not take place, or else, after it occurs, the second polar body "comes back" and fuses with the mature gamete. Both possibilities are compatible with the observations. In the mouse, the first possibility appears to have been proved (Eppig et al.).

Early work on the chromosomal complement of teratomas was concerned with establishing the presence of sex chromatin in teratoma cells. According to Ashley approximately one third of teratomas of the testis in males have been found to contain cells with sex chromatin, which is taken to indicate the presence of two X chromosomes, one of which has undergone inactivation. Data on extragenital teratomas have remained scanty. Chromosome studies are often hampered by the frequent presence of aneuploidy in cultured teratoma cells. However, the finding of a sex chromatin mass in a substantial proportion of testicular teratomas (Ashley; Hunter and Lennox; Martineau) is of interest. If parthenogenetic fusion of two haploid gametes is proposed as the origin of teratomas, one would expect the female zygote to be always XX. The male, however, having cells of either X or Y chromosomal constitution, could produce zygotes of either XX, XY, or YY type, in a ratio of 1 (XX) to 3 (XY+YY) (Hunter and Lennox). Assuming all YY cells to be unviable, the expectation would be 1 (XX) to 2 (XY). Contrary to these anticipated results, some early reports showed up to 48 percent of teratomas in males to be XY, whereas in females, teratomas from various sites were always sex chromatin-positive (Warkany). The chromosomal complement of teratomas from various sites yielded heterogeneous results: some were uniformly sex chromatin-positive, others negative, and still others of "mosaic" type. The latter finding was used as an argument to rule out parthenogenesis as an explanation for the occurrence of "female" (chromatin-positive) teratomas in male individuals. In an editorial comment on the work of Linder, Gerald noted that arrest in meiosis II, as postulated for ovarian teratomas, would produce, in the testicle, either XX or YY cells. Since only the former are viable, teratomas of the testis that are not sex chromatin-positive would have to arise by a different mechanism. Parthenogenetic fusion of two haploid cells might produce, in the male, sex chromatin-positive (XX) tumor cells (Martineau). Kaplan and associates recently reported that 5 of 6 human *extragonadal* teratomas had the same karyotype as the host. They favored origin from diploid mitotic cells; sex chromatin-positive tumors, in their opinion, may result from polyploidy.

Phenotyping of enzyme markers by electrophoresis was used by Linder and others (Kaiser McCaw et al.; Linder et al.; Linder and Power) to approach this problem, taking advantage of the fact that glucose-6-phosphate dehydrogenase (G6PD) is known to be X-linked. In the female, one of the two alleles is randomly inactivated. Therefore, when these investigators found that cells from a sacrococcygeal teratoma were heterozygous for G6PD, they concluded that the tumor cells had originated from two or more progenitor cells after X-inactivation. The electrophoretic phenotypes showed either A or B bands, indicating origin from either A or B cells; there was no hybrid AB band, which means that the possibility of both alleles being simultaneously active may be ruled out. Among the tumors phenotyped by Linder and associates was an example of a neoplasm with a yolk sac carcinoma component that was found to have an XY chromosomal pattern. This was interpreted as consistent with mitosis, not meiosis, at the time of inception. Hence, the available evidence, albeit limited, is compatible with the proposition that gonadal and extragonadal teratomas may have different modes of origin. Ashley attempted to reconcile many of the previously discussed theoretical and experimental concepts by proposing a hypothesis of origin of teratomas that admits four possible pathways. The cell of origin is an undifferentiated cell that has retained "full genetic capacity," i.e., potential for multiple tissue differentiation. Ashley thought that this cell could be either a germ cell within the gonad, a germ cell that has become sequestrated in an ectopic site during embryonic life, or an embryonic cell that has escaped the activity of organizers, and which is likely to be present in the midline of the embryonic body. This undifferentiated cell might form tumors directly. Such teratomas would show cells of diploid chromosomal complement, and would be heterozygous in a manner exactly equivalent to that of the normal tissue of the host. Secondly, teratomas could originate after the undifferentiated cells underwent meiosis, and then restored the diploid number of chromosomes by reduplication within the cell. Such tumors would be diploid and homozygous for all chromosomes and all loci. Thirdly, teratomas could originate by fusion of two cells that have become haploid after meiosis. Cells resulting from this fusion would be analogous to zygotes, and therefore diploid and heterozygous for chromosomal polymorphisms in a manner different from that of the host. Fourthly, a haploid cell might fuse with a diploid cell. The resulting tumor cell would be triploid and would have a number of complex heterozygosities, which would differ from those of the host.

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Epidemiologic Data on Human Teratomas

However ill-defined, the pathologic process that accounts for the onset of teratomas is believed to occur during embryonic life. Accordingly, most extragonadal teratomas become clinically manifest soon after birth, or in the childhood years. Fraumeni and associates reviewed the death certificates of children who died of cancer in the United States from 1960 to 1968, and supplemented their study with a review of the hospital records of 198 children with teratomas cared for at 11 major medical centers for the treatment of children's neoplasms. Among the conclusions derived from that study, are the following:

- Under 15 years of age, the mortality due to teratomas is three times higher in girls than in boys.
- Between 15 and 19 years of age, there is a predominance of boys, but this applies only to white children; among nonwhites, girls still predominate.
- There is a peak in mortality from teratomas at 1–2 years of age, reaching a death rate of over 2.0 per 1,000,000 per year in girls, and less than 1.0 per 1,000,000 per year in boys. Death rates then decline, and gradually rise again after age 6 in girls. In boys, a rapid rise occurs after age 14, which greatly exceeds the leveling female rate.
- There was no correlation between the occurrence of teratomas and season-of-birth, geographic distribution, or siblings with malignant tumors.

The predominance of females with teratomas contrasts with the general excess of males with childhood neoplasms (Ederer et al.; Fraumeni et al.). The increased death rate that is observed in adolescence is clearly due to the appearance of testicular teratoma in this age group. Even though such an occurrence is less common than the appearance of teratomas in the ovary, it carries a serious prognostic connotation. It should be noted that testicular tumors in general appear to be less frequent in Negroes than in Caucasians (Mostofi). This difference in racial distribution is particularly marked in the case of testicular teratomas. In a study conducted among the Igbos of Nigeria, of 86 teratomas collected in a central laboratory over a period of six years, none was of testicular origin (Onuigbo). Comparative studies of individuals who have a common ethnic background but who live in different parts of the world are of importance to delineate the relative participation of genetic and environmental factors in the onset of neoplasia. One such study (Olisa et al.) compared the relative frequencies of malignant tumors in American black and Nigerian children. Again, the rarity of gonadal neoplasms of presumptive germ cell derivation was confirmed for black children living in Washington, D.C.: the most common teratoma of this group of patients was ovarian (3.1 percent) and no testicular neoplasms were observed.

During infancy and childhood, prior to the emergence of a relatively high number of gonadal tumors, a sacrococcygeal location is uniformly acknowledged as the most common form of teratomas (Anees and Reddy; Bale et al.; Berry et al.; Carney et al.; Fraumeni et al.; Grosfeld et al.; Gross et al.). Thus, the early peak in the mortality curve for teratomas is almost entirely accounted for by sacrococcygeal teratomas, whereas the later peak is due to gonadal, particularly testicular, teratomas. Sacrococcygeal teratomas remain, at all ages, the most common of extragonadal teratomas. Thus, of 58 teratomas in patients under 16 years of age collected at the Mayo Clinic between 1935 and 1965, 22 were sacrococcygeal, and there was an insufficient number of cases of other locations to be certain about sex-related anatomic preferences (Carney et al.). Of 91 cases seen in 35 years at the Hospital for Sick Children in London, 63 percent were sacrococcygeal. A compilation of various published case series of teratomas, reported from institutions of different geographic sites is presented in Table 2.

The high prevalence of sacrococcygeal teratomas in early life, and the enhanced frequency with which these tumors are responsible for deaths due to extragonadal teratoma, should not obscure the fact that youth is also a factor in gonadal teratomas of malignant nature. Of 471 ovarian neoplasms, excluding follicular cysts, metastatic tumors and rare tumor types, seen in persons younger than 20 years, 238 (50.5 percent) were benign cystic teratomas; 93 (19.8 percent) were malignant teratomas, and 38 (8.1 percent) were dysgerminomas. Among 4292 tumors of the ovary found at all ages, 1041 (24.2 percent) were benign cystic teratomas; 17 (0.4 percent) were malignant teratomas, and 7 (0.2 percent) were dysgerminomas (Mulligan). These figures indicate that the ratio of benign to malignant teratoma of the ovary is 2.5 to 1 below the age of 20 years, as compared to 60 to 1 when all ages are considered. The interpretation advanced by Mulligan that induction of mature, benign tissues requires the development of a normal cyclic function in ovarian follicles not involved by tumor, appears plausible.

It appears that the frequency of occurrence of germ cell tumors has been subject to variations in different world populations. Extragonadal teratomas have not been studied in this respect. In the experience of the British Testicular Tumour Panel, the incidence of testicular teratomas rose

Table 2

PRIMARY ANATOMIC SITE OF TERATOMAS
(SERIES FROM PEDIATRIC INSTITUTIONS)

AUTHOR AND YEAR	GEOGRAPHIC SITE	NO. OF CASES	Head (Extra Cran)	Neck	Mediast*	Retroper*	Ovary*	Testis*	Sacrocc*	Abdom	Perineum	CNS
Bale et al., 1975	Comperdown, Australia	107	6	10	5 (1)	7 (3)	16 (4)	7	51 (9)			5 (3)
Mambo, 1975	Salisbury, Rhodesia	29		3		1	3		19 (3)	1	2 (2)	
Berry et al., 1969	London, England	91	2	3	5	1	10	7 (1)	58 (10)	2		3
Grosfeld et al., 1976	Indiana, USA	85		3	10	3	8 (3)	2 (2)	59 (11)			
Carney et al., 1972	Minnesota, USA	58	1		17 (3)	3	5 (1)	3 (1)	22 (6)			7 (3)
Onuigbo, 1976	Enugu, Nigeria	86		1			74 (2)		11			
Anees and Reddy, 1970	Kurnool, India	41				1	26 (3)	10	3 (1)			1
Mahour et al., 1974**	California, USA	81	1		3 (1)	4	30 (4)	5	36 (5)	1†		1
TOTAL AND PERCENT BY SITE		578	1.7%	3.4%	7%	3.4%	29.7%	5.8%	44.8%	0.69%	0.34%	2.07%

*Number in parenthesis indicates malignant cases.

**From Mahour, G.H., Wooley, M.M., and Trivedi, S.N. Teratomas in infancy and childhood: experience with 81 cases. Surgery 76:309-318, 1974.

†Case primary in the umbilical cord.

from 0.4 per 100,000 males in 1958, to 1.26 per 100,000 males in 1971 (Pugh and Cameron). This rise appears to be part of a trend toward increased mortality from testicular tumors that has been observed in a number of countries throughout the world. Such an increment has been noted in Denmark (Clemmensen), New Zealand (Howden), the United States (Grumet and MacMahon), and, more recently, in Japan (Lee et al.). There is no evidence that this increase encompasses Negro patients, whose general refractoriness to develop germinal neoplasms has been alluded to before. Also, according to Mostofi and Price, the increased incidence of testicular tumors has been seen in adult patients, whereas pediatric populations have apparently remained unaltered in this respect. Extragonadal teratomas originate mainly in children, yet comparable figures do not exist for extragenital teratomas. It has been known for some time, however, that particular anatomic forms of teratomas occur with a definite preference for individuals of one or the other sex (e.g., gastric teratoma in males), or in certain ethnic groups and geographic areas (higher incidence of intracranial teratomas in Japan). In order to avoid repetition, a consideration of the incidence and conditions of occurrence of teratomas of different anatomic localizations will be presented in the introductory paragraph of the respective chapter.

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BENIGN OR MALIGNANT? A PRACTICAL APPROACH

The decision as to the benign or malignant nature of a given case largely rests on the identification of primitive, undifferentiated cells and tissues within the tumor. This general statement, however, must be qualified by the following considerations:

1. Embryonal carcinoma cells

Experimentally, it has been shown that in the early phases *all* teratomas contain primitive, undifferentiated cells that cannot be distinguished morphologically from malignant cells. Accordingly, the experimentalist resorts to nonmorphologic technics, such as the tumor's capacity to be retransplanted into an isogeneic host, in order to define the benign or malignant nature of the tumor. Regrettable as it might seem to the reflective intellect, the methodology of the basic researcher is not routinely applicable to diagnostic problems in man. Examination of tissues by conventional histologic methods continues to be the mainstay in the laboratory diagnosis of tumors in clinical medicine. Moreover, experience has shown that certain morphologic patterns possess undeniable predictive value. The identification of these immature tissues and their proportion within the tumor thus acquire primary importance.

2. Germ cell tumor cells

The relative prognostic significance of the different types of immature or undifferentiated tissues, is not the same. Thus, immature somatic tissues have variable prognostic expectations, whereas areas of "germ cell tumor," i.e., germinoma (seminoma or dysgerminoma), choriocarcinoma, embryonal carcinoma, and yolk sac tumors, are always malignant. Choriocarcinoma has long been recognized to associate with a malignant, rapidly progressive course in teratomas. It is becoming increasingly apparent that the presence of endodermal sinus tumor dictates a comparably grim prognosis. Several studies (Ballas; Talerman) have underscored the malignant character of testicular teratomas with an endodermal sinus tumor component. Length of survival has been tentatively related to the amount of yolk sac carcinoma within the tumor (Parkinson and Beilby). Evidence is available that points to an equally unfavorable association in the case of ovarian teratomas (Beilby and Parkinson), and our own experience has shown that in sacrococcygeal teratomas, the presence of yolk sac carcinoma almost invariably results in a teratoma of rapid progress and high frequency of metastases (Gonzalez-Crussi et al.). In sum, the totipotential cells of origin of teratomas may remain undifferentiated (embryonal carcinoma), or embark upon lines of differentiation of extraembryonic elements, either vitelline (yolk sac tumor) or trophoblastic (choriocarcinoma). Any of these possibilities carries with it somber prognostic connotations. Whereas one of the histologic patterns ordinarily becomes predominant, and may become the sole morphologic aspect of the tumor, their coexistence in a given case is theoretically possible. Kurman and Norris have identified a neoplasm, in the ovary, that showed both vitelline and trophoblastic differentiation, and which they likened to embryonal carcinoma of the testis; by the light of the histogenetic concepts mentioned above, this neoplasm represents an "extraembryonic teratoma" of mixed nature. Such a terminology has been recently advocated (Jimerson and Woodruff).

3. Germinoma cells

The presence of areas of germinoma (seminoma or dysgerminoma) requires a special comment. The histogenesis of this tumor has been a subject of dispute. In consequence, its relationship to teratoma has also been debated. Initially, it was held that seminomas or dysgerminomas arise from primitive gonadal cells that are unipotent, having lost their competence to differentiate into teratomatous elements, and capable of reproducing only their own kind. In support of this idea were the observations that seminomas of the testis originate within seminiferous tubules, and that when seminoma and teratoma coexist they may be separated by a capsule, or, if both appear admixed, no transitional stages between the two types of tissue can be seen. More recently, most authorities have maintained that while germinomas and teratomas are distinctive neoplasms, both arise from a primitive multipotent germ cell. As stated earlier (see Classification of Gonadal and Extragonadal Teratomas. Use of Terms in Pathologic Diagnosis), this concept of histogenesis prevails currently. The ability for multiple tissue differentiation is not apparent in the majority of germinomas, whose morphology remains uniform. However, on occasion a tumor indistinguishable from seminoma or dysgerminoma will produce metastases of unquestionably teratomatous character, will seem to blend with embryonal carcinoma, or will show foci of choriocarcinomatous differentiation. Hence, it must be assumed that germinoma cells possess the same competences as embryonal carcinoma cells, and must be regarded as representing an initial stage in differentiation of primitive multipotent germ cells. Accordingly, the presence of germinoma areas in a teratoma should be considered prima facie evidence of malignancy, as is the case for choriocarcinoma, embryonal carcinoma, or yolk sac tumor. It is a tribute to the effectiveness of modern therapy that the patient's prognosis is not uniformly poor for all these neoplasms. Germinomas are malignant tumors, yet very radiosensitive. Modern forms of combined therapy can often achieve effective control. There is no evidence to show that when the seminoma forms part of an otherwise well differentiated teratoma, its response to therapy would be any different.

A determined effort should be made by the pathologist to identify germ cell tumor patterns, and to mention their presence in the final diagnosis of a teratoma. In the past, these appearances were referred to as simple "undifferentiated" areas, or named "carcinomatous" areas, "papillary carcinoma," or "adenocarcinoma," using these designations in a loose way. This practice obscured the correct identification of the specific neoplastic tissues that contribute to worsen the prognosis, and the effect that therapy has upon them. The presence of biochemical "markers" in embryonic tissues constitutes another strong argument for the proper identification of such tissues in a teratoma. At the time of this writing, embryo-specific proteins are being increasingly used for initial diagnosis of the tumor, or for diagnosis of otherwise inapparent metastatic deposits and for monitoring the effects of therapy. Whereas gonadotropic hormone (HCG) and alpha-fetoprotein (AFP) are currently the substances most often investigated in malignant teratomas, other products, such as transferrin and alpha-1-antitrypsin (Tsuchida et al.), receive some attention. The recent isolation of pregnancy-specific β-glycoprotein from plasma and tissue extract in a patient with testicular teratoma

(Johnson et al.) is only one example of the modern concern to establish, by means of biochemical and immunochemical technics, a functional profile of the embryonal tissues found in teratomas. Ultimately, these data should be correlated with morphologic observations, and the cellular origin of tumor products traced by appropriate technics.

4. Nongerminal tumor cells

Aside from the distinctive patterns of embryonal carcinoma, germinoma, and extraembryonic tumor tissue differentiation, teratomas may contain a number of incompletely differentiated somatic tissues that reproduce the process of organogenesis in the embryo. The significance of such morphologic appearances in a teratoma has been debated.

Neuroectodermal derivatives are among the most commonly encountered tissues in teratomas. Often, they appear immature and reproduce the morphology of neuroblastoma in various stages of differentiation. We believe that, as in neuroblastoma, this primitive tissue has the capacity to differentiate to mature nervous tissue without invasive proclivity. Very rarely, primitive neurogenic tissue has been known to disseminate and give rise to hematogenous metastases (Gonzalez-Crussi et al.). In such exceptional cases, the presence of prominent neuroepithelial tubules has rendered the histologic appearance somewhat unlike that of typical neuroblastoma. The rarity with which metastatic spread occurs probably does not justify any attempts to introduce further therapeutic measures in those cases subjected to complete surgical excision and devoid of germ cell tumor components. On the other hand, the fact that distant spread has, however rarely, taken place, should preclude an attitude of complacency: extensive areas of immature somatic tissues in teratomas are a formal indication for close postoperative follow-up of the patient. Norris and associates have duly stressed that pathologists should cease looking for recognizable sarcoma or carcinoma patterns, overlooking the fact that the immature tissues are the malignant ones. Regrettably, the conditions under which either maturation or enhanced tumor proliferation take place are at present unknown. In consequence, the pathologist's contribution to a prognostic evaluation consists mainly in identifying the component neoplastic tissues and estimating their quantitative proportion. The usefulness of assessing the relative amount of immature somatic (nongerminal) tissues present in teratomas has been repeatedly shown (Gonzalez-Crussi et al.; Robboy and Scully; Thurlbeck and Scully). This is the basis for histologic grading, as discussed later.

Information is even more scanty with respect to the natural history of other immature tissues found in teratomas, such as undifferentiated mesenchyme, nephrogenic tissue, embryonic-appearing lung components, etc. The creation of a national center of reference for centralization of experience would be a worthwhile endeavor that could contribute to solving these questions. Repository centers for concentration of case material already exist that have shed new light on the clinicopathologic correlations of different tumor types. Because of the extremely complex histology of teratomas, the implementation of a systematic analysis is likely to be facilitated by a concerted effort of similar kind. In the meantime, our conduct should be subordinate to the major premise that the immature tissues are potentially malignant tissues. Furthermore, it must be recalled that, in contrast to gonadal teratomas which are tumors of adult patients, the extragonadal teratomas frequently occur in children. Thus, the typical appearances of carcinomas and sarcomas of adults that most pathologists are used to identifying, are found only uncommonly as part of a teratoma. As a practical guide, and drawing from the experience of various national cancer study centers, we advocate conscientious sampling of teratomas for histopathologic examination: at least one section per centimeter of the largest diameter of the tumor, or ten sections, whichever number is greatest, from most specimens. A more meticulous search is warranted when there is clinical or intraoperative suspicion that specific areas of the tumor may be at higher risk of malignancy. In addition, the gross appearance of the tumor might serve as a guide for more thorough sampling when soft, "fleshy," necrotic areas are present, or when an invasive manner of growth is detected.

Correlation of Grade and Prognosis

When a teratoma that had been considered to be fully differentiated is later found to metastasize, it is usual to demonstrate immature tissues in the metastases. The assumption is then that immature tissues were initially present that were missed in the sampling. A few cases of testicular teratoma are known, however, in which a well differentiated (so-called "adult") teratoma gave rise to equally well differentiated metastases (Kedia and Fraley). This occurrence has not been well documented in primary extragenital teratomas, but, assuming a common origin, such an observation is certainly possible. Even the confirmation of these rare cases, however, would not invalidate the usefulness of grading; it would merely demonstrate that histopathologic grading cannot *exclusively* be relied upon for estimating prognosis. In contrast, the generally excellent correlation found between clinical staging and histologic grading is useful to gauge the outcome of the disease.

Subclassification of Teratomas

From the foregoing, it should be apparent that a useful systematization of teratomas should be guided by the following major premises:

i) The presence of a germ cell tumor component worsens the prognosis. Such areas should be indicated in the pathologist's report.

ii) Incompletely differentiated tissues are potentially malignant. Their specific nature and amount should be indicated in the pathologic diagnosis.

Agreement on these central concepts, however, has not resulted in uniformity of nomenclature and diagnostic guidelines. The British Testicular Tumour Panel (Pugh and Cameron) uses the following terms:

Malignant Teratoma, Trophoblastic (MTT), for tumors of the testis that contain choriocarcinomatous elements, regardless of how large or small these areas may be, and however well differentiated the rest of the tumor may be. This acknowledges the poor prognosis of trophoblastic differentiation in a teratoma. Hence, teratomas that express this type of differentiation are grouped into a separate category, or MTT. The rest of the teratomas are graded by the most highly differentiated areas, as follows:

Teratoma, Differentiated (TD), for teratomas composed entirely of differentiated tissues and cells, in which no areas of histologically malignant components are present.

Malignant Teratoma, Intermediate (MTI), For teratomas with both differentiated and undoubtedly malignant areas.

Malignant Teratoma, Undifferentiated (MTU), for teratomas in which there is absence of organoid areas and differentiated structures. Usually their structure is made up of cell masses of carcinomatous appearance.

This classification was devised for testicular teratomas, and grades teratomas by the most highly differentiated tissues. As Pugh states: "Two teratomas, one nine-tenths MTU and one-tenth TD, and the other with the proportions exactly reversed, will both be MTI." It might seem paradoxic that tumors of widely divergent histology could be classified together, and that this classification could offer useful prognostic information. Nonetheless, European workers have provided justification for its use (Robboy and Scully). Criticism was voiced by Mostofi and Price. They took issue with the lack of provisions to indicate specific cell types, and considered "MTT" an inadequate substitute for choriocarcinoma. Heretofore, there has been no successful effort to classify all teratomas, regardless of primary site, in a comprehensive way. The following tentative classification is offered as an attempt to reconcile the experience gained from the study of primary gonadal teratomas with observations on the pathology and natural history of their extragenital counterparts. I am indebted to Dr. Kent Mancer, of the Toronto Sick Children's Hospital, for his suggestions.

CLASSIFICATION

I. BENIGN TERATOMAS:

A. Mature Teratoma:

- Grade 0 (All component tissues appear well differentiated).
- Grade 1 (Occasional microscopic foci contain incompletely differentiated tissues, not exceeding 10 percent of the sampled surface).

B. Immature Teratoma, Benign:

- Grade 2 (Immature tissues make up between 10 and 50 percent of the sampled tumor surface).
- Grade 3 (Over half the surface examined is composed of undifferentiated tissues of uncertain metastatic potential. A benign course is still possible).

II. MALIGNANT TERATOMAS:

A. With Areas of Germ Cell Tumor:

- Germinoma (seminoma, dysgerminoma)
- Embryonal carcinoma
- Choriocarcinoma
- Yolk sac tumor
- Mixed (any combination of the above)

B. With Non-germinal Malignant Tumor Pattern:

- Carcinoma
- Sarcoma
- Malignant embryonal tumor
- Mixed

C. Immature Teratoma, Malignant:

- A teratoma that would otherwise be classified as benign immature teratoma, but which subsequently became metastatic.

It is not superfluous to reiterate that a prognostic estimate is an effort to synthesize all the clinical and laboratory information under a single concept. Of primary concern to the morphologist is the nature of the tissues composing the tumor, and their amount and disposition within the material examined. The pathologist, however, should avail himself of all other circumstances made known to him, i.e., the patient's age, sex, rate of tumor growth, and site of the primary tumor, if he is to emit a personal opinion about the benign or malignant nature of a given case. In so doing, he is not placing blind trust in morphology, but attempting empirical generalizations made possible by medical experience. To illustrate, the diagnosis "mature teratoma of the orbit, benign," derives its credibility not so much from demonstrated proof of a correlation between histology and prognosis (the universal validity of this is apparently denied by the example of metastatic "adult" teratoma), but from the knowledge that there have been many instances of orbital teratomas that remain confined, and none metastasizing, and that this occurrence is likely to repeat itself in a fresh instance of similar morphology. Otherwise stated, the prognosis implies an application of the inductive principle, closer to be found true the wider the inductive basis on which it is formed.

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TERATOMAS OF THE SACROCOCCYGEAL REGION

SYNONYMS AND RELATED TERMS: Middledorpf tumor; sacral parasitic fetus; trigerminal teratoma of the sacrum; teratoid sacral tumor; presacral teratoma; sacral teratomatous twin; presacral choristoma; sacral teratoma; sacrococcygeal teratoid tumor; ventral sacral tumor; ectopic cerebroma.

General Considerations. Teratomas of the sacrococcygeal region may arise anterior to the sacrum and grow toward the pelvis, or they may originate mainly posterior to the sacrococcygeal bones, and grow outside the pelvic cavity. The names "presacral" and "postsacral" teratoma have been used to denote the respective topographic relationship. The pathologic anatomy of these tumors, however, is the same regardless of their location; furthermore, a sizable proportion of these tumors show combined presacral and postsacral patterns of growth (see below). Accordingly, teratomas of the sacrococcygeal region will be discussed collectively in this section, in the belief that they share a common, albeit unknown, etiology. This statement should be partly qualified by the recent description of a familial syndrome of presacral teratomas, even though the number of cases is still too low to conclude that the site of origin of the tumors should be made a criterion for classification. As described by Ashcraft and associates, the syndrome, present in 23 patients of six investigated kindreds, consists of: presacral teratoma growing in the hollow of the coccyx and extending upward to the pelvis; skeletal sacrococcygeal defects; postanal abscesses, and skin dimpling at the site of attachment of the tumor; a transmission pattern suggestive of dominant inheritance, with approximately equal distribution among males and females, and low incidence of malignancy. Only 1 of 19 resected tumors was malignant, and several patients had associated urinary tract anomalies.

The distinctly familial distribution of the lesions signifies that genetic influences may be operative in the genesis of at least some of the cases of sacrococcygeal teratoma. Other reports have mentioned a familial occurrence of sacral defects coexistent with sacrococcygeal teratoma (Conklin and Abell; Eklöf; Kenefick) without firm identification of a clinical syndrome. On the other hand, sacrococcygeal teratomas have been noted in progenitor and offspring (Smith et al., 1979), without mention of the rest of the components of the syndrome.

The postsacral or extrapelvic growths are the most common. Since these tumors are often very conspicuous at birth, documented observations antedate the beginning of the Christian era; although it is understandably difficult to be certain of the diagnosis, Pantoja and Rodriguez-Ibañez trace recorded cases to the remotest antiquity. It has been known for some time that sacrococcygeal teratomas are the most common teratomas of infancy and childhood. This does not mean that the pediatrician in practice will encounter them frequently, as the incidence varies in different studies between 1 in 30,000 to 1 in 170,000 births (Dillard et al.; Grosfeld et al.; Miles and Stewart). For reasons that remain unclear to our days, female infants largely predominate: approximately three-fourths of the patients are girls (Altman et al.; Dillard et al.; Donnellan and Swenson; Gross et al.; Izant). A history of twinning in the families of patients with sacrococcygeal teratoma is said to be a frequent finding in some case series (Gross et al.; Hendren and Henderson), but in others it is either absent or not recorded (Carney et al.; Grosfeld et al.; Gwinn et al.). This is a question that is in need of rigorous statistical analysis, as it bears on the hypothesis that maintains that teratomas are suppressed twins or parasitic fetuses. Also in need of precise ascertainment is the frequency and specific nature of other diseases seen in association with sacrococcygeal teratoma. Whereas over 90 percent of infants born with these tumors are the product of full-term gestation (Altman et al.), mention of "associated conditions" is sometimes made.

Izant found that over one-third of his patients presented other pathologic conditions together with the teratoma. The associations include: adenomatous polyps of the rectum, hemivertebrae, soft tissue sarcoma, coccygeal defects, and omphalocele. In a case report of a 39 year old woman operated on for sacrococcygeal teratoma (Leslie et al.), mention was made of a family history of hemophilia; there were seven pairs of twins in 71 pregnancies along four complete generations in the family of the propositus. Many other reports, exclusively concerned with certain clinical and pathologic features of these tumors, omit any allusion to associated conditions in the patients harboring the teratomas. A survey conducted among the surgeon members of the American Academy of Pediatrics (Altman et al.) showed that 18 percent of 405 patients with sacrococcygeal teratoma had associated congenital anomalies, a figure greatly in excess of the 2.5 percent rate anticipated in an unselected population. The organ systems most commonly involved were, in decreasing order of frequency: musculoskeletal, renal, and nervous. Least common were cardiac and intestinal anomalies, each having equal frequency. The same survey failed to show any relationship between birth weight and tumor; sacrococcygeal teratomas were equally prevalent among infants of all weights. It is unlikely that congenital anomalies contribute very significantly to the mortality of infants with sacrococcygeal teratoma, since the majority of the associated congenital abnormalities are regarded as not life-jeopardizing by themselves (Altman et al.; Gonzalez-Crussi et al.). Conklin and Abell reported a 20 percent rate of coccygeal aplasia and sacral malformation, but the family history of the patients was not investigated. It has been suggested that when osseous malformations are found, they may indicate the familial form of teratoma (Davidson).

Sacrococcygeal teratomas in adult patients are comparatively rare. Marcuse collected 15 cases from published reports appearing between 1900 and 1950. Killen and Jackson tabulated and analyzed the clinicopathologic features of 37 cases in 1964. Only 24 cases were found in the English language literature between 1952 and 1974 (Miles and Stewart), and few have appeared since (Head et al.). Less than 10 percent of all sacrococcygeal teratomas are detected in adults. However, most patients give a history of symptoms, or of presence of a mass, since infancy or childhood. Therefore, the assumption is that all sacrococcygeal teratomas presenting in adults had their inception before birth, though they may have escaped detection in early life. Indeed, draining sinuses, abscesses (Haidak and Bates), and protuberant tumors of the sacral area have been neglected by some patients for over three decades (Leslie et al.; Mears), and mild tenesmus or vague abdominopelvic discomfort for an even longer time. Increased medical education of the public and enhanced awareness of the manifestations of these tumors among the medical profession might contribute to reducing the number of cases allowed to pursue such a protracted course.

All the general characteristics thus far discussed undoubtedly reflect biologic phenomena that may be factors of importance in the etiology of sacrococcygeal teratoma. Unfortunately, none has been defined with the scientific rigor that would enable the application of preventive measures. Thus, beyond the statement that features such as female predominance or familial history express "a role of heredity" in the genesis of these tumors, nothing of greater clarity may be said to define what this role may be. Environmental factors possibly also play a role, but at the present time their nature is equally vague. Caspi and Weinraub described the appearance of sacrococcygeal teratoma in a newborn infant whose mother had been treated for sterility with high doses of human gonadotropins. Regardless of the precise mechanism of production of teratomas (see Pathogenesis), gonadotropins were deemed capable of stimulating favorable conditions for its occurrence. A recent case report documents the association of sacrococcygeal teratoma in a stillborn female infant, and administration of acetazolamide, a carbonic anhydrase inhibitor, to the mother for the treatment of glaucoma (Worsham et al.). The drug was taken daily for years, and was discontinued at 19 weeks' gestation. Although a cause-and-effect relationship was not proposed, the authors discussed the experimentally demonstrated teratogenic potency of this drug in animals. The inception of sacrococcygeal teratomas may result from an interplay between environmental influences and local factors unique to this anatomic area (see Teratomas in Monkeys). More information must be accumulated concerning environmental factors suspected of playing a role in the origin of teratomas. Sacrococcygeal teratomas are tumors of worldwide occurrence. Although the relative frequency of involvement of different ethnic groups is difficult to ascertain, case series and isolated reports have originated from all continents, and have been drawn from all racial groups (Bale et al.; Berry et al.; Gonzalez-Crussi et al.; Izant and Filston; Nwako and Ezi-Ashi; Renoirte et al.; Tseng et al.; Walls). The number of recorded cases is now in the thousands. It is likely that centralization of experience might facilitate a more rational analysis of data pertinent to the elucidation of the etiology and pathogenesis of this disease.

Clinical Features. The presence of a mass visible on external examination is the usual presenting complaint. Growth may be so spectacular as to justify graphic descriptions of "large tumors with attached small infants" (Salaymeh). Such utterances faithfully convey the first clinical impression in the not too unusual instances in which the weight of the tumor approaches or surpasses half the weight of the baby. Not surprisingly, these large teratomas may be responsible for difficult births and obstetrical accidents with injury to mother, neonate, or both (Neal and Carlisle; Schiffer and Greenberg; Tribble; Walls). In the vast majority of cases the tumors are not diagnosed prenatally, and are discovered with surprise in the delivery suite. There usually is no diagnostic difficulty when confronting such obvious cases (figs. 10–13), but the small, or the inconspicuous neoplasms, heavily tax the diagnostician's acumen. At times, a small area of inappropriate skin, a barely visible discrepancy in the fullness of

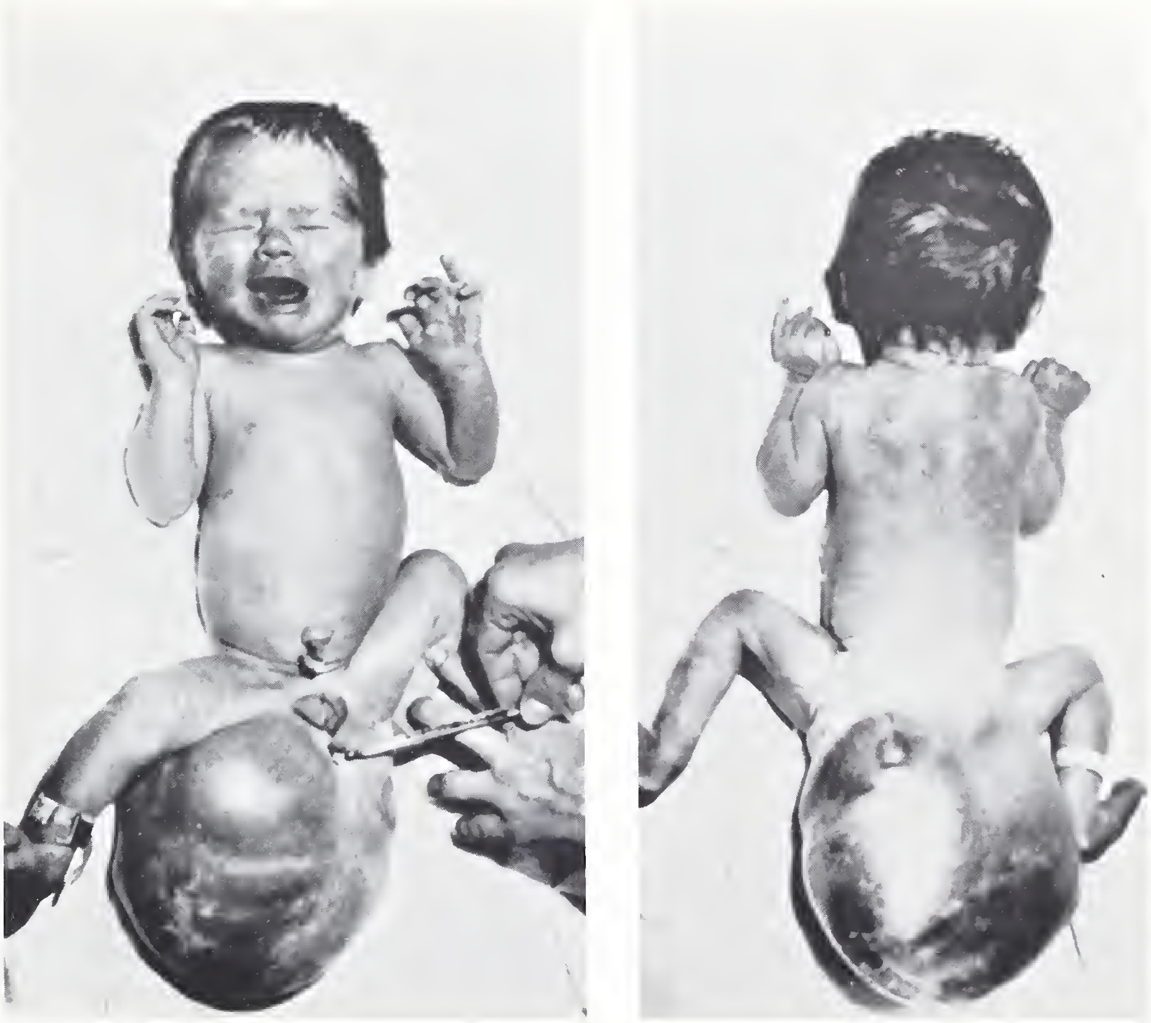

Figure 10
SACROCOCCYGEAL TERATOMA
Congenital sacrococcygeal teratoma with large extrapelvic growth. (Courtesy of Dr. Jay L. Grosfeld, Indianapolis, IN.)

the buttocks, a tail-like appendix (fig. 14), or even a dimple or depression in the soft tissues of the area, may be the sole indication of the presence of an underlying teratoma. This is especially true of those tumors that present beyond the neonatal period.

The survey of the Surgical Section of the American Academy of Pediatrics (Altman et al.) ascertained four major types of growth in these tumors:

Type I, the most common, is external, i.e., outside the pelvis ("postsacral" or "retrosacral"). This was seen in 186 of 397 patients examined. The tumor presents as a mass hanging between the infant's legs, as if in continuation of the trunk (figs. 10, 11). This type of growth associates with a benign course in many, but not all, cases; none of the patients in this group had metastasis when first seen.

Type II tumors are "dumbbell" growths, with roughly equal presacral and extrapelvic volume. Six percent of these cases had metastases when first diagnosed.

Type III is "asymmetrical dumbbell," with predominance of the presacral, or intrapelvic growth. Although Type III cases were between four and five times less common than either Type I or Type II, they are

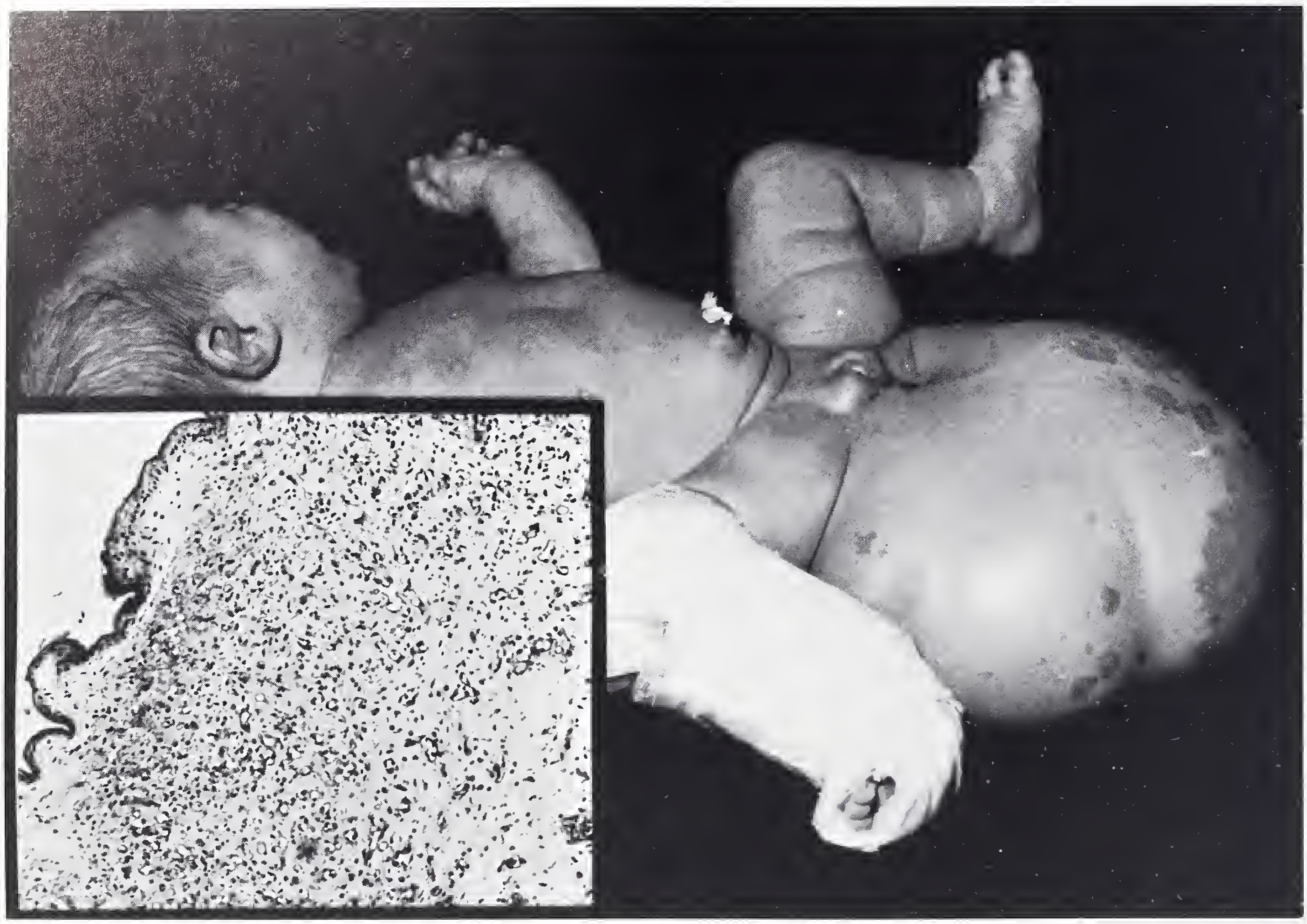

Figure 11
SACROCOCCYGEAL TERATOMA
Sacrococcygeal teratoma associated with pes valgus. Hemangiomatous changes are present on the skin overlying the tumor. Inset shows excessive capillary-sized blood vessels in the dermis. X90.

much more aggressive. Twenty percent of Type III cases had distant metastases at the time of diagnosis.

Type IV teratomas grow entirely in the sacral hollow, without an external component. Eight percent of Type IV tumors presented with evidence of metastases.

Of all teratomas in the sacrococcygeal region in infants and children, 5 percent had metastases at the time of diagnosis (Altman et al.). The American Academy of Pediatrics Survey was conducted by means of mailed questionnaires to surgeons. It yielded no information on the type of tissue present in the malignant teratomas, or on the correlation between the clinical course and the histologic composition of the tumors.

Tumors with intrapelvic growth are more difficult to diagnose, and delay in discovery of inapparent masses may partly account for the more sinister outlook of the inconspicuous tumors. Delayed diagnosis and treatment do not wholly explain, however, the more ominous prognosis of certain teratomas. An inherently enhanced power of proliferation, however ill-defined, must be proposed to account for the fact that the most malignant group of tumors in the quoted survey was not purely intrapelvic, or Type IV group, teratomas. Presumably, this inherent capacity for excessive and disorderly proliferation is reflected in a Type III growth: that is, indiscriminate growth in all directions as a result of intrinsic constitutional attributes of the tumor.

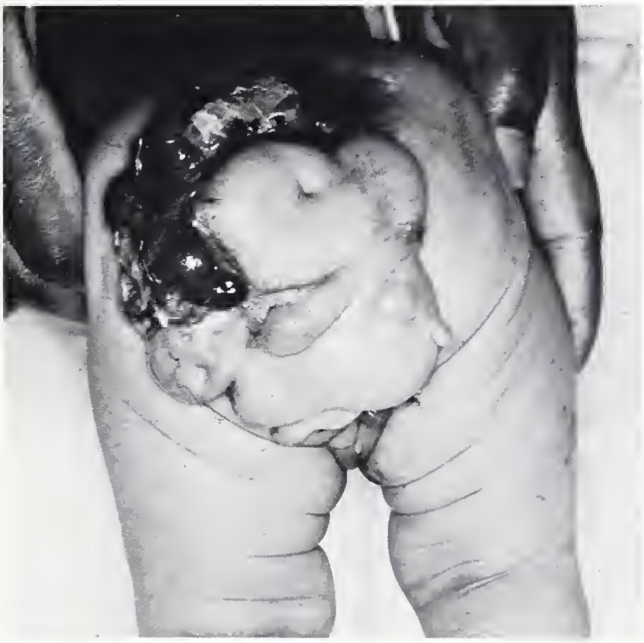

Figure 12
SACROCOCCYGEAL TERATOMA
Extensive ulceration and hemorrhage of skin in a congenital malignant teratoma.

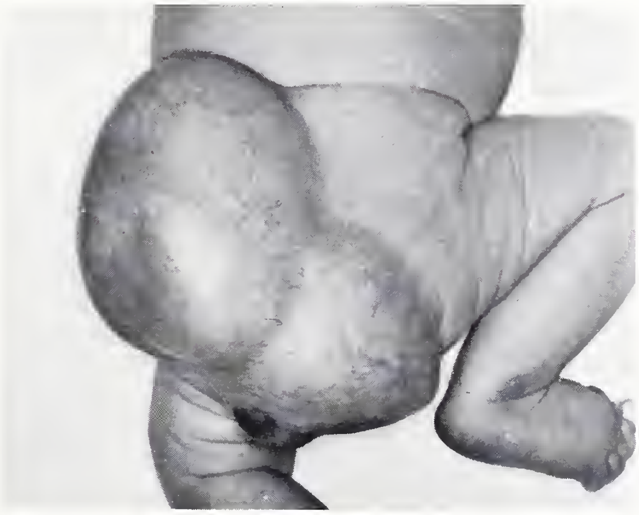

Figure 13
SACROCOCCYGEAL TERATOMA
Sacrococcygeal teratoma with coexistent meningocele. (Courtesy of Dr. Jay L. Grosfeld, Indianapolis, IN.)

The skin overlying the conspicuous tumors may be uniformly smooth and tense, or may show roughened patches, or large, distended vessels; at times, the skin covering the tumor shows a distinctly hemangiomatous appearance (fig. 11). Necrosis and ulceration of the covering skin and perineal structures is a complication that may occur during or after birth (fig. 12). In the past, infants whose tumors became complicated in this manner often succumbed to infection and sepsis (Ravitch and Smith). Modern treatment and precocious surgical intervention have reduced this hazard, but skin breakdown followed by severe hemorrhage is still a potentially lethal development (Riker and Potts), and the risk of infection in a debilitated infant should not be minimized. Hemorrhage may be more dangerous when associated with a hemangiomatous appearance of the covering skin (Donnellan and Swenson). The large size and cystic nature of many of these tumors may facilitate internal bleeding within preformed cystic cavities; sudden shock with inapparent blood loss may therefore occur. Such bleeding may take place during birth (Schiffer and Greenberg).

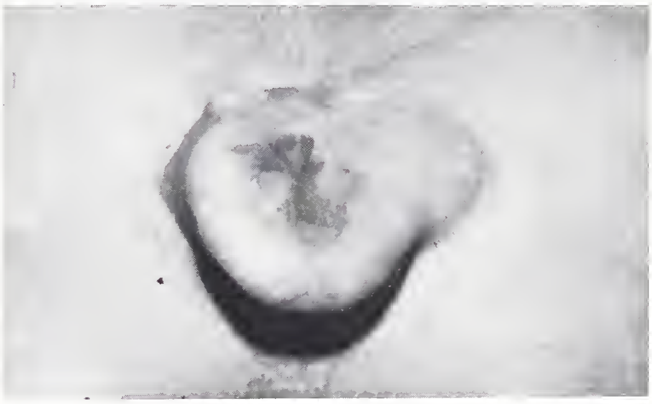

Figure 14
SACROCOCCYGEAL TERATOMA
Tail-like appendix covered by hairy skin at the site of a small sacrococcygeal teratoma. (Courtesy of Dr. W. A. Donnellan, Chicago, IL.)

Prominence of one buttock may be a sign of an underlying teratoma. Asymmetry of this area could reflect the lateral extension of a tumor over the ipsilateral iliac wing; Donnellan and Swenson admonished that in such cases the surgeon should be aware of the possibility of intrapelvic tumor growth through the lesser sciatic notch. An intrapelvic teratoma may be suspected when there is deformity and forward deviation of the anal orifice. Skin discoloration (Walker and Foster), hemangioma, or hairy nevus (Scobie) may also announce the presence of a hidden tumor. All these outward signs should be carefully looked for because, like many other retroperitoneal tumors, the intrapelvic portion of a sacrococcygeal teratoma may grow to massive dimensions without giving rise to symptoms. Moreover, the inability of infants and small children to verbalize their complaints behooves the clinician to sharpen observation: an infant may be seen to purposefully avoid a certain position, or to experience discomfort when inadvertently moving into that position. Under these circumstances careful palpation of the perineum and rectal examination are mandatory; the latter procedure is sometimes advocated as routine practice of the comprehensive physical examination of neonates. Neurologic examination should be carefully performed to rule out a meningocele as cause of the sacrococcygeal mass. Neural defects may coexist with sacrococcygeal teratoma.

Among the uncommon forms of presentation of sacrococcygeal teratoma are systemic manifestations not directly attributable to the presence of the mass. Hydramnios has sometimes been present. Idiopathic hydrops fetalis has been reported at least once (Kohler) in association with sacrococcygeal teratoma; none of the conditions known to occur with fetal hydrops were present. Since hydrops fetalis has also been noted in a case of mediastinal teratoma (Macafee et al.), it was speculated that protein sequestration by the tumor, or disproportionate increase in the vascular territory may have been instrumental in provoking hydrops. Such explanations can only be conjectural today. Less difficulty exists in explaining endocrinologic disorders. The endocrine tissues composing a teratoma are potentially functional, so that the occasional reports of endocrine dysfunction, such as precocious puberty (Omenn; Rhoden) or hyperadrenocorticism (Waldhausen et al.), may be attributed to hormonal output by the neoplastic tissue. The fact remains that in many cases glandular tissue is morphologically identifiable in the tumor, but the patient does not evince manifestations of endocrinopathy. In the vast majority of cases the presence of a mass and its physical effects dominate the symptomatology, overshadowing all but the most severe disturbances caused by humoral secretion of tumor cells.

Compression effects are prone to develop in teratomas with important intrapelvic growth (Gwinn et al.; Izant and Filston). A barium enema may then show anterior displacement of the rectum. Another complication is obstructive uropathy. Hydronephrosis, hydroureter, and severe bladder distention may be seen with sacrococcygeal teratoma (Gwinn et al.). Obstructive uropathy ordinarily indicates intrapelvic extension of the tumor. Regardless of the benign or malignant nature of the neoplastic tissue, obstruction to the urinary tract is a serious complication that may pose technical problems in removal of the tumor, and may cause death from uremia. Massive abdominal distention due to urinary ascites, secondary to ureteral obstruction by the tumor, has been described as a rare clinical presentation (Scatliff and Abernathy). Another infant required colostomy, cystostomy, and change of sex-of-rearing because a malignant sacrococcygeal teratoma had grown in such a way as to encircle the urethra of a hypospadic penis (Uehling et al.).

Laboratory and Roentgenologic Examination. The explosive development of research on the immunologic characteristics of experimental teratoma raises the hope that, in the future, immunochemical methods may provide diagnostic information of great reliability and enhanced sensitivity. At the time of this writing, determination of alpha-fetoprotein (AFP) in the serum of patients with sacrococcygeal teratoma has proved to be the laboratory test that most commonly correlates with a malignant clinical course. Elevated values generally portend a bad prognosis (Gonzalez-Crussi et al.; Grosfeld et al.), as they may reflect the presence of a yolk sac tumor (endodermal sinus tumor) component, a feature of particularly grim forebodings in teratomas in general (Brown). Gitlin and Boesman established that embryonic endoderm, yolk sac and liver cells normally synthesize AFP during intrauterine development. Theoretically, the presence of islands of liver tissue in a teratoma could also produce substantial elevations of AFP. Liver tissue, however, is rarely identified in sacrococcygeal teratomas, and a sustained elevation of this embryo-specific protein is deemed a reliable indication of the presence of yolk sac tumor. It is advisable to look for a persistent elevation, given that AFP is a normal biosynthetic product of hepatocytes during fetal life; hence, interpretation of questionable AFP rises in samples collected soon after birth, may be difficult. Tumor-associated AFP is usually of an order of magnitude well above marginal increases; furthermore, this protein is of great value in the detection of recurrent, or metastatic tumor. The normal adult may have between 4-16 ng. of AFP in the serum, the newborn infant 3-4 ng.; with tumors, AFP may be elevated hundreds or thousands of times above these levels (Teilum).

The pronounced nature of the elevation has permitted antenatal diagnosis; in one case, AFP was detected in the amniotic fluid obtained by amniocentesis (Schmid and Mühlethaler), and a stillborn infant with sacrococcygeal teratoma and multiple malformations was delivered days later. The malformation did not include defects of neuroectodermal tube closure, so that it may be assumed that the AFP gained the amniotic cavity by exudation from the tumor. No mention was made of the state of the skin covering the tumor.

Hunt and associates have discussed the radiographic findings of the hereditary presacral teratoma syndrome. Other than the presence of a teratoma, the main radiologic features were bone defects of the sacrum and coccyx occurring in a familial pattern. The osseous defects varied in severity from subtle abnormalities involving only part of the coccyx to extensive bilateral sacrococcygeal defects. One peculiarity of these familial cases was the absence of radiologically visible calcifications in the teratomas. In some patients there was evidence of vesicoureteral reflux. A low frequency of malignancy in this syndrome has been alluded to before, but complications are sometimes serious: one of these patients died from meningitis complicating an anterior meningocele (Davidson).

Most patients with sacrococcygeal teratoma have the nonfamilial form of tumor.

Plain x-ray films are of fundamental importance in the diagnosis, but barium enema, excretory urography, and voiding cystourethrography may be required to better evaluate the extent of the disease (figs. 15–17). Plain films may establish the presence or absence of associated bone defects, and of calcifications within the tumor parenchyma. Schey and co-workers saw calcifications in benign teratomas four times more often than in malignant ones. In like manner, benign teratomas were more often cystic than their malignant counterparts. None of these features can give absolute certainty about the benign or malignant nature of the tumor. The presence of calcifications merely increases the preoperative diagnostic assurance that one is dealing with a teratoma. Diagnostic confidence is also enhanced when it is apparent that the tumor is multicystic, as can be suspected by radiography or sonogram.

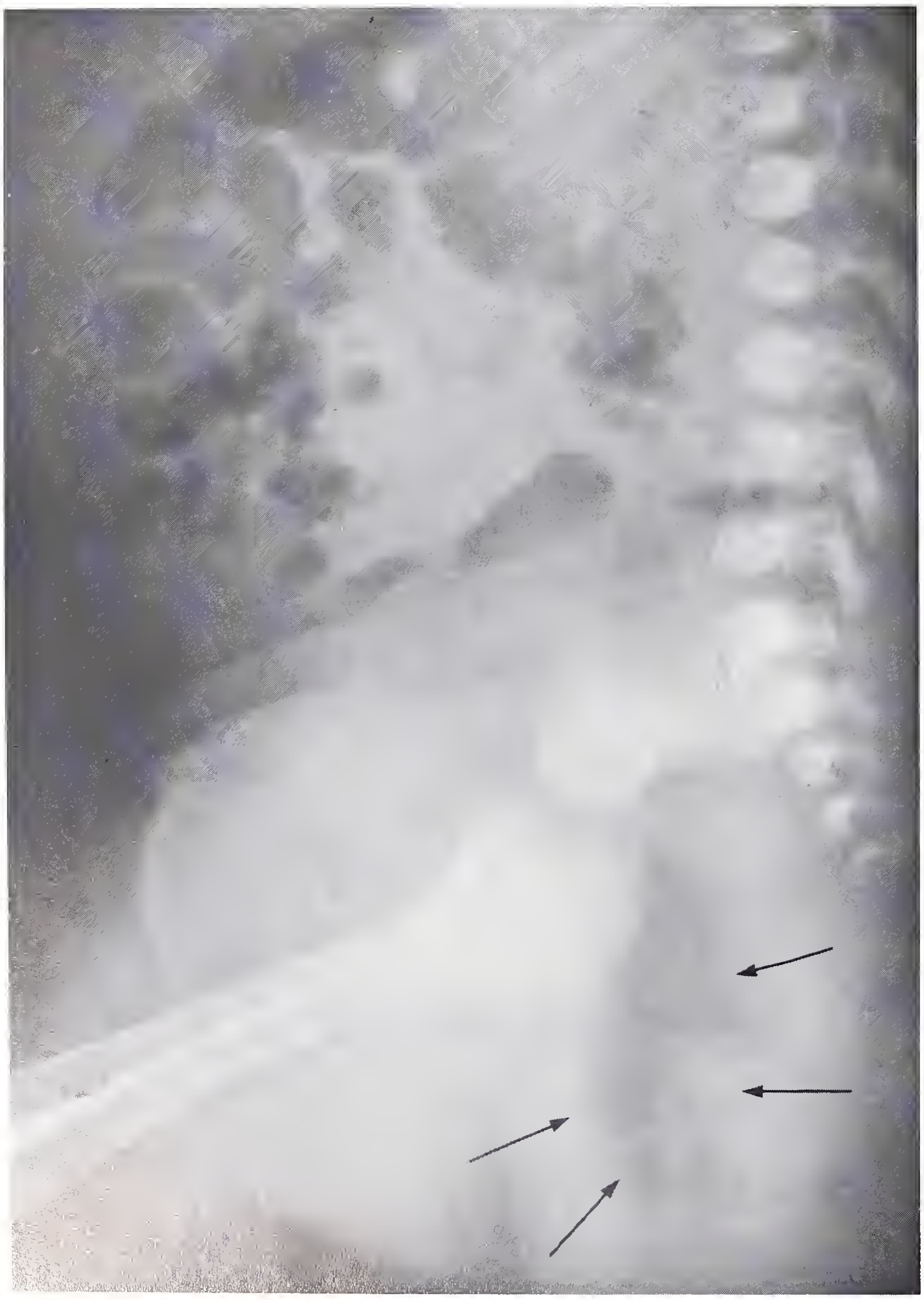

Figure 15
SACROCOCCYGEAL TERATOMA
Sacrococcygeal teratoma with intra- and extrapelvic growth. The appearance of a soft tissue mass with focal radiolucencies (arrows) suggests the multicystic nature of the tumor and permits prediction of its histology. (Courtesy of Dr. E. Franken, Indianapolis, IN.)

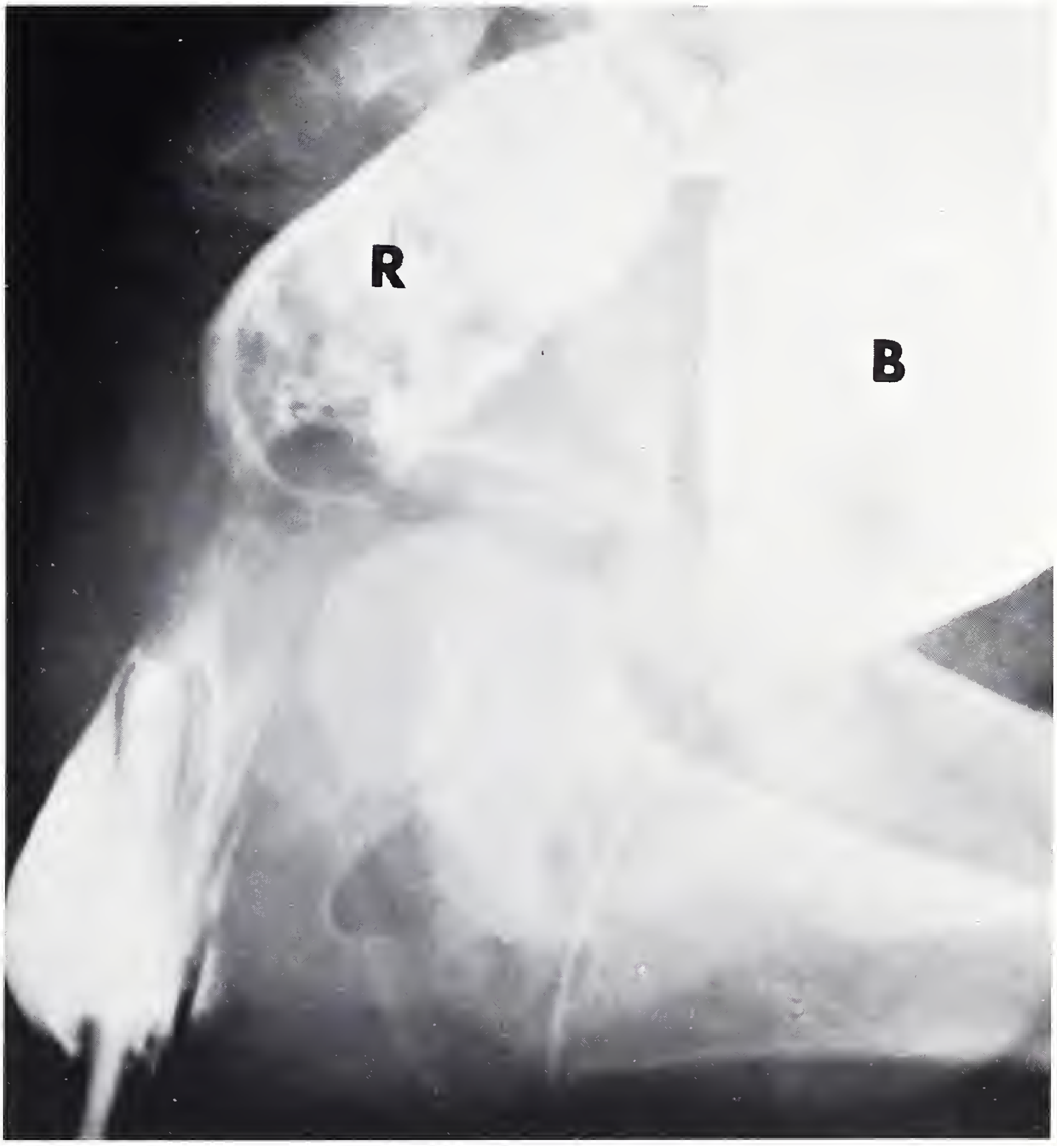

Figure 16
SACROCOCCYGEAL
TERATOMA

Intrapelvic growth of a malignant sacrococcygeal teratoma is indicated by widening of the space intervening between bladder (B) and rectum (R). The relative position of these organs is best visualized with the aid of contrast medium.

Ultrasound technics have helped to establish the prenatal diagnosis of these tumors (Zaleski et al.). Injection of air, or carbon dioxide, after fluid aspiration, has been advocated as a useful means of ascertaining the size of the cysts and their possible communication with the spinal canal (Scatliff and Abernathy). The diagnosis of teratoma is virtually certain when bones or teeth are visualized inside the mass (Willox and MacKenzie), but the benign or malignant nature of the teratoma must always be verified by histopathologic examination.

Roentgenograms are especially helpful in the distinction between meningocele and teratoma. Spina bifida or other vertebral anomalies favor a diagnosis of meningocele, but these skeletal anomalies may be present together with a teratoma (Gruenwald). Meningocele may also coexist with teratoma in the same patient, in which cases severe lumbosacral osseous malformations may be evident. Severe dysraphic states and meningocele or lipomeningocele have been known to occur in association with malignant teratoma. It has been speculated that these instances represent delayed malignant transformation of teratomatous tissue which was chronically "irritated," or in some manner interacted with the dysraphic

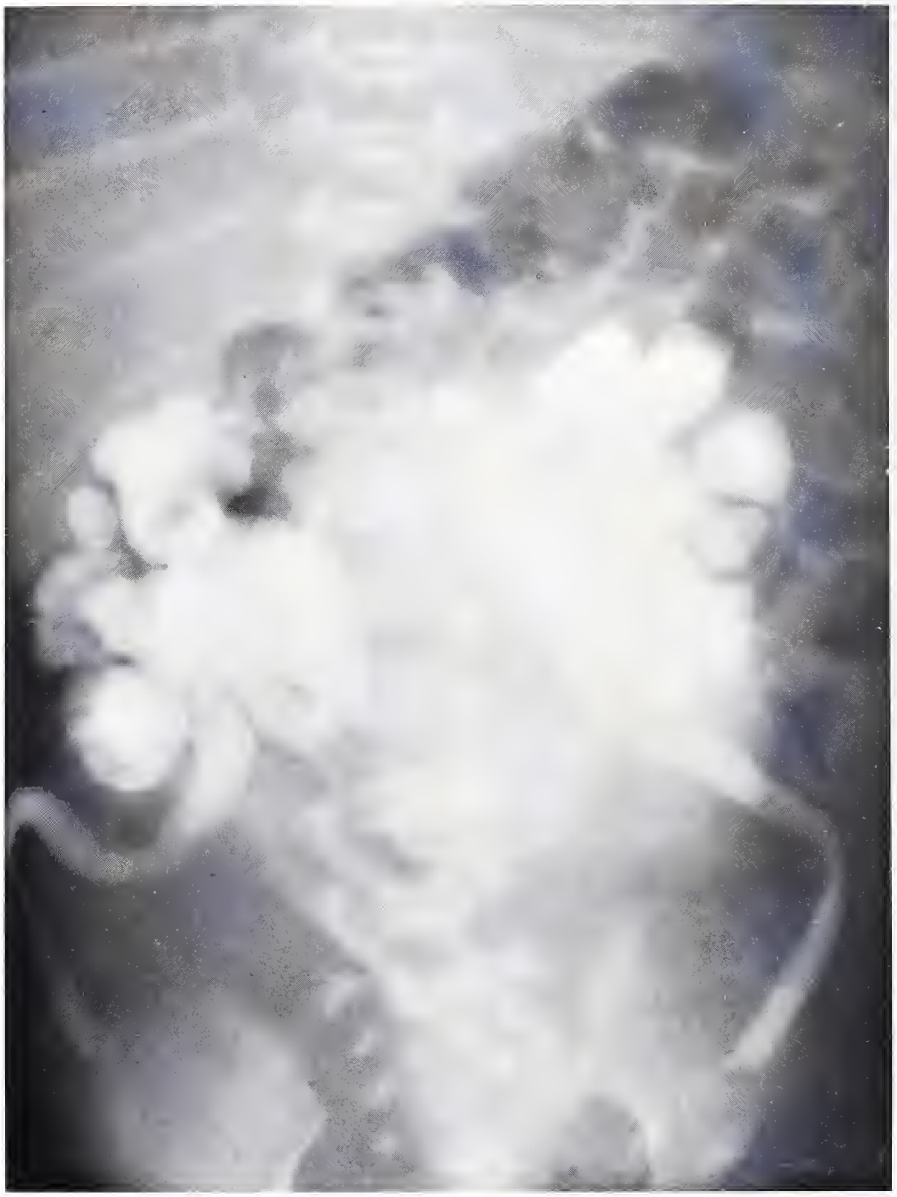

Figure 17
SACROCOCCYGEAL TERATOMA
Intravenous pyelogram shows anterolateral deviation of ureters and severe bilateral hydronephrosis secondary to intrapelvic sacrococcygeal teratoma. (Courtesy of Dr. E. Franken, Indianapolis, IN.)

lesion over a period of years (Mickle and McLeenan). From the standpoint of the roentgenologic distinction between meningocele and teratoma, specialized studies, including myelography, may be required to best delineate the existing pathology (Pantoja et al.). Laminography may be of importance in cases of suspected intraspinal extension, because pressure effects within the vertebral canal, vertebral pedicles, and arches have been observed (Dillard et al.). Angiography is acknowledged as a definite asset to estimate the degree of vascularization of the tumor and the specific anatomy of the main feeding vessels. The risk of surgical accidents may be decreased by prior knowledge of the tumor's vascular supply. Most commonly, the tumor derives its blood supply from the midsacral arteries (Smith et al., 1961) or hypogastric arteries (Priebe).

Routine ultrasonographic examination of pregnant women has been able to visualize the presence of a mass attached to the sacral area of the fetus, which by its solid appearance may suggest the diagnosis of teratoma prenatally (Zaleski et al.).

The most frequent problem to be resolved by roentgenographic examination in infants and children is distinction from myelomeningocele. In adults, other conditions must be ruled out. Primary bone tumors, such as giant cell tumor or chordoma, may originate in this anatomic area, but these lesions are apt to produce roentgenographic images characteristic of intraosseous lesions either on plain films or with multidirectional tomography; computerized tomography further assists in demonstrating extraosseous extensions (Smith et al.). However, a sacrococcygeal teratoma that has remained untreated for a long time, or that has undergone malignant transformation, is capable of producing bone destruction (Marcuse) of uncertain radiographic appearance. In neonates, abnormal sacral ossification may be due to the presence of a large tumor compressing the sacrum (Scatliff and Abernathy). Regardless of the patient's age, a thorough roentgenographic study is a safeguard against unpleasant surprises at surgery: an inappropriate surgical approach for tumors of improperly defined extent has been one of the most regrettable (Pantoja et al.). Anomalies of fixation of the rectum may result in anterior rectal deviation simulating extrinsic compression (Lawson et al.), and operations have been performed without finding a mass.

Gross Appearance. These tumors appear as sharply delimited or encapsulated masses. There may be an intimate relationship with the coccyx in spite of apparent good demarcation. In contrast, adhesions to the pelvic viscera are not commonly encountered unless secondary inflammatory changes have occurred (Gross et al; fig. 18).

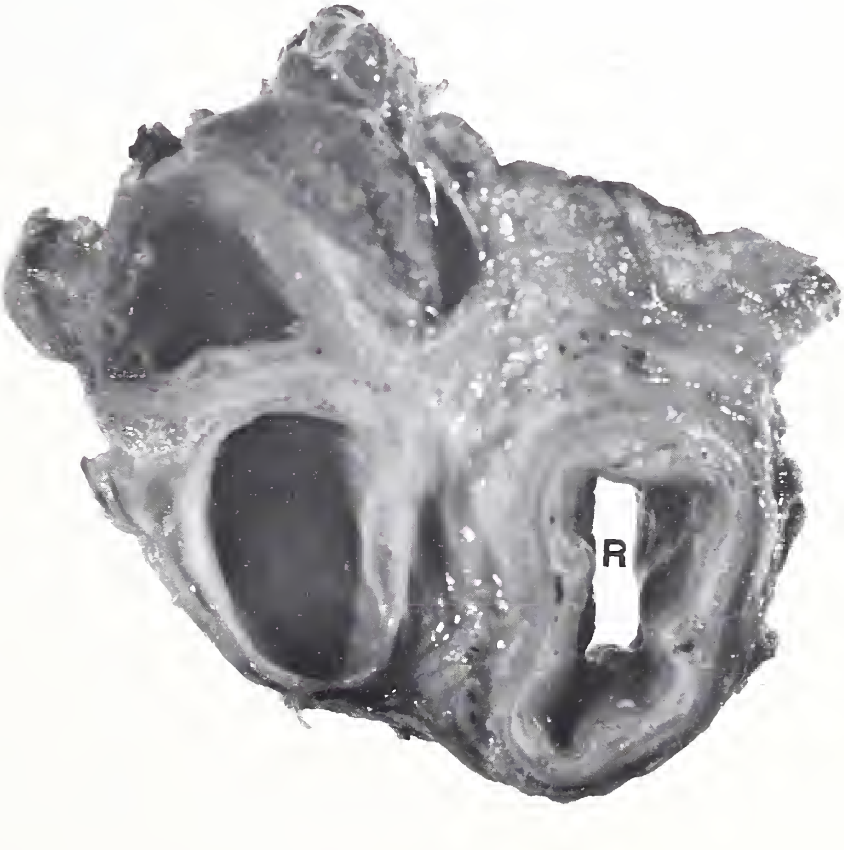

Figure 18
SACROCOCCYGEAL TERATOMA
Recurrent sacrococcygeal teratoma with dense attachment to the wall of the rectum (R). Note the well formed cysts, which microscopically were lined by different types of epithelium.

Cysts are grossly recognizable in the tumor parenchyma; their contents may be serous, mucoid, or hemorrhagic (fig. 19). Certain examples of sacrococcygeal teratoma are striking to the observer because of the complexity of structures that may develop within the tumor; complete digits with joints, skin, and nails (Nicholson), lengths of intestine, limb components (fig. 20), external male genitalia (Sharma et al.), and well formed teeth have been observed.

Due to the presence of very large fluid-containing cysts, evacuation of the fluid may be followed at times by marked decrease in volume. The emptied tumor may then resemble a crumpled, skin-covered bag (fig. 21). On the skin surface, there may be areas of atrophy, hyperkeratosis, hemangioma, ulceration, nevus, etc.; often the skin appears smooth and tense without associated pathologic condition. The pathologist must try to identify the coccyx in all operative specimens. The coccyx may be adherent to the tumor, and this may indicate the presence of invasive, malignant tissue, or extracapsular spread of benign-appearing teratomatous elements (fig. 22). In some cases, dense adherence to the rectum may require extensive surgery (fig. 18). A predominantly cystic tumor will be found to be more commonly benign; teratomas consistently solid, with practically

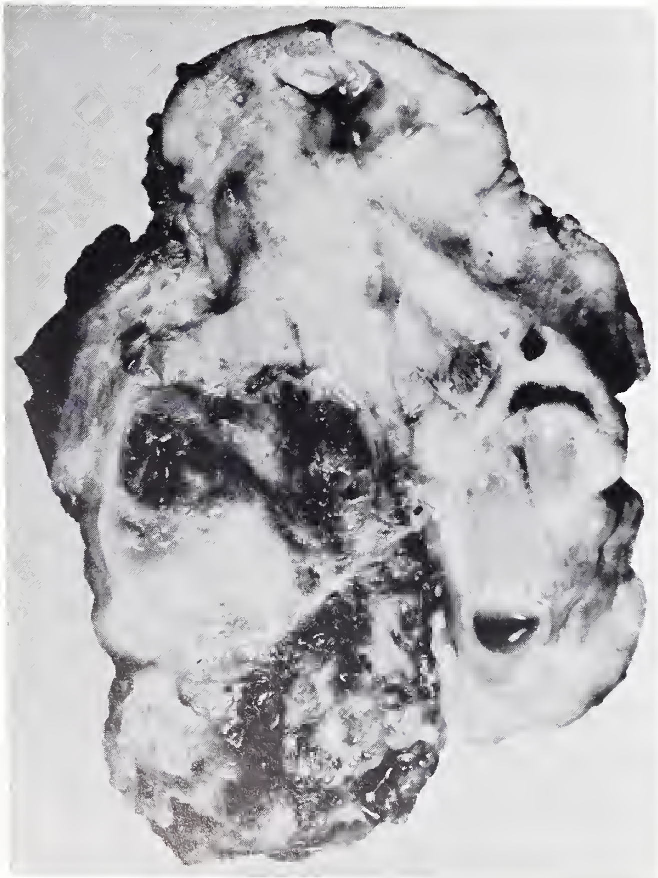

Figure 19
SACROCOCCYGEAL TERATOMA
Cut surface of predominantly solid, benign sacrococcygeal teratoma.

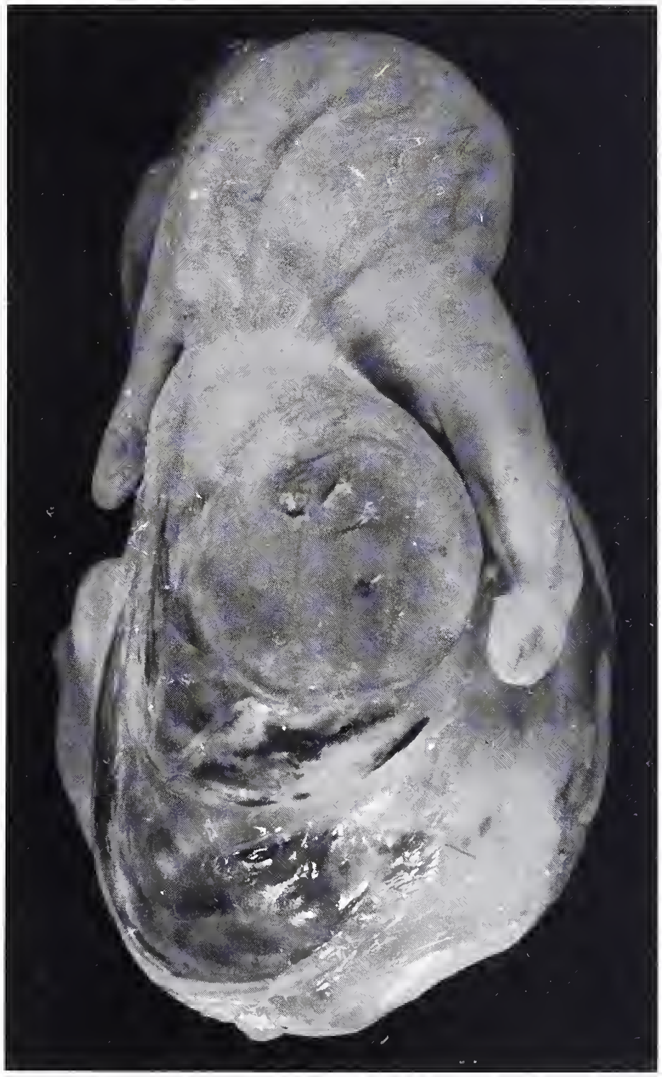

Figure 20
SACROCOCCYGEAL TERATOMA
Sacrococcygeal teratoma with limblike protrusions and a hemicranium. (Courtesy of Dr. C. Nézelof, Paris, France.)

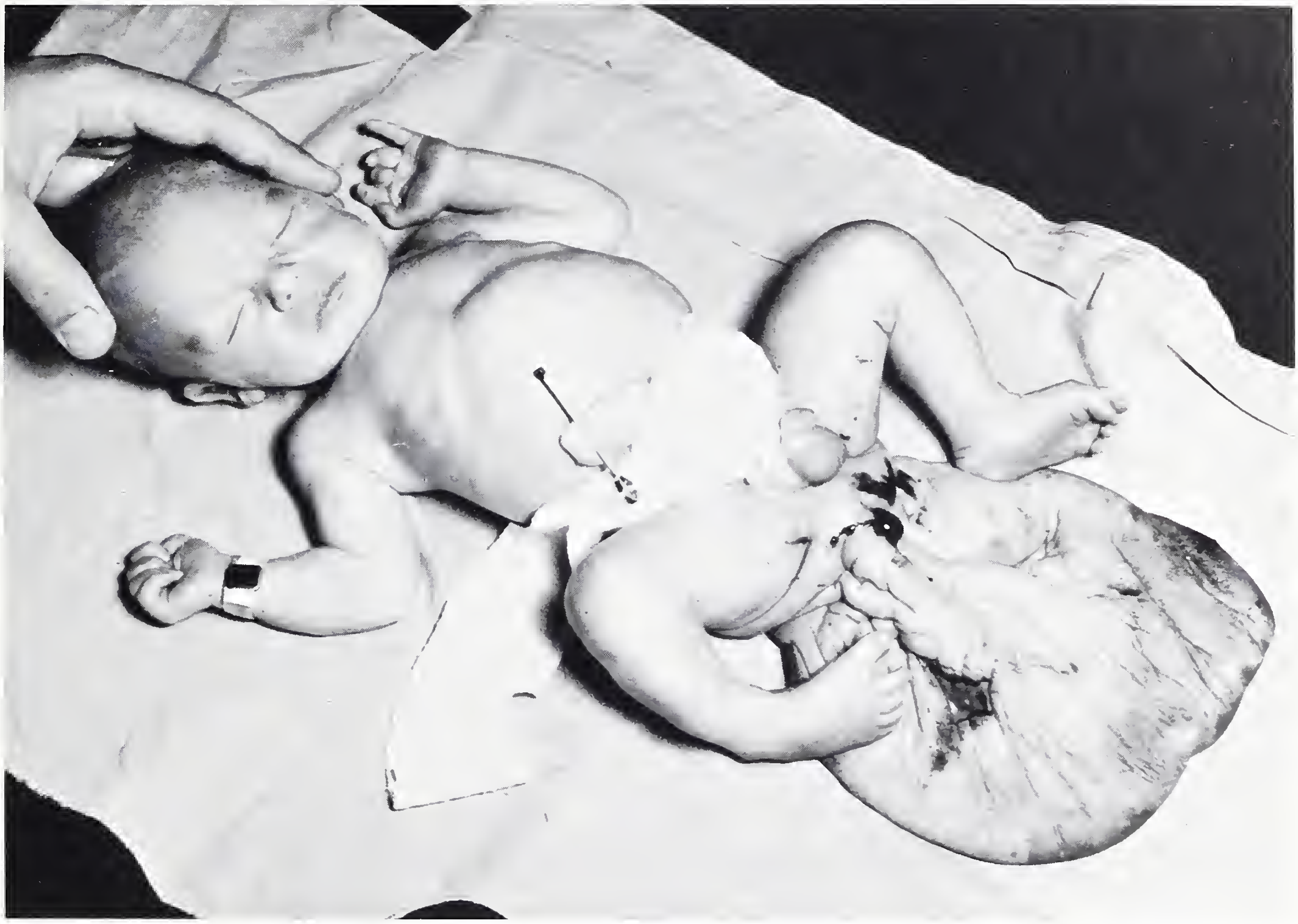

Figure 21
SACROCOCCYGEAL TERATOMA
Large pedunculated and largely cystic sacroccygeal teratoma. "Crumpled bag" appearance after evacuation of its fluid contents through accidental rupture during birth. (Courtesy of Dr. J.M. Kissane, St. Louis, MO.)

no cystic components, are more liable to be malignant. None of these gross features is entirely reliable, and under no circumstances should they take the place of histologic examination in making a judgment about the benign or malignant nature of a particular case (fig. 19).

Microscopic Appearance. In contrast to spontaneous or induced teratocarcinomas of the mouse, in which organs of complex morphogenesis such as kidney, lung, or liver have not been observed, human sacrococcygeal teratomas can form an impressive variety of tissues (figs. 23–26). This diversity of composition has given rise to a comparison of the caudal end of the fetus with a "Sargasso Sea" (Moersch). Reviewers have been too prompt to conclude that one or another type of tissue "does not occur" as part of the sacrococcygeal teratoma, only to see their statement contradicted by subsequent reports. Thus, claims that Betz's cells, liver, or myocardium appear "never to be present" in these tumors (Donnellan and Swenson) have had to be revised with the appearance of additional descriptions.

In spite of the tissue heterogeneity of these tumors, the malignant component is overwhelmingly of the yolk sac tumor type. The presence of this tissue explains

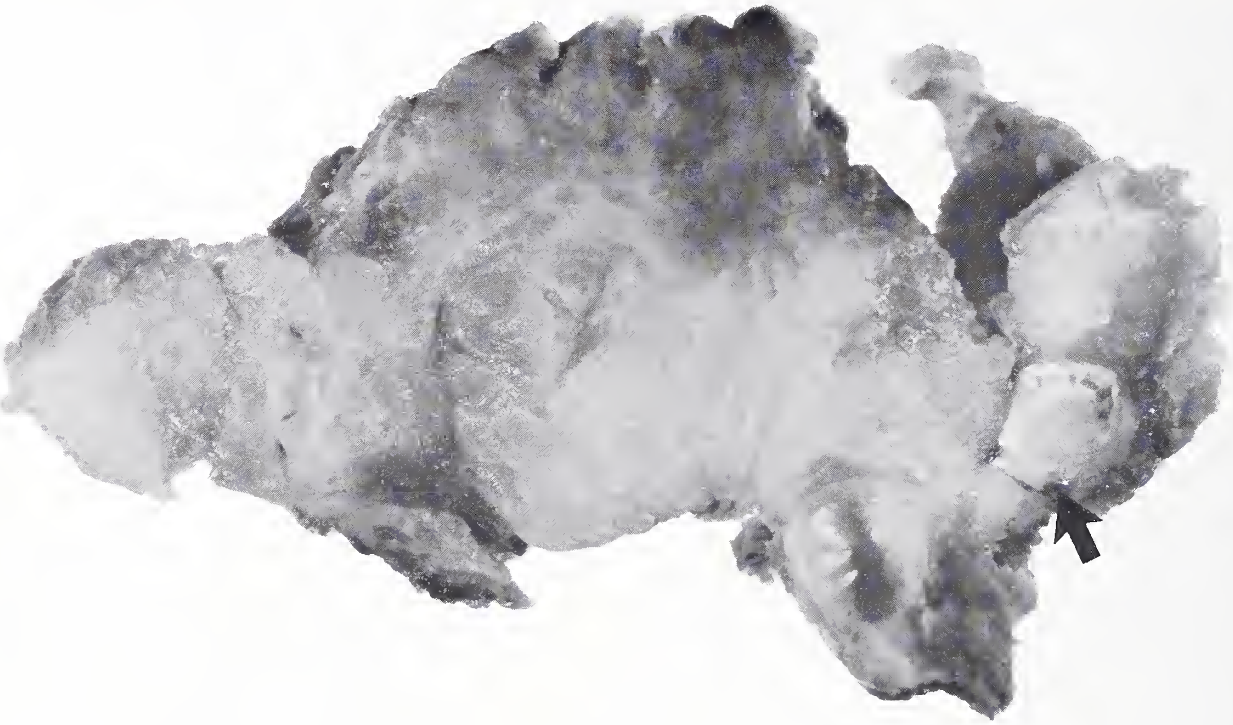

Figure 22
SACROCOCCYGEAL TERATOMA
Operative specimen of recurrent sacrococcygeal teratoma. Dense attachment to the coccyx (arrow) illustrates the need for en bloc resection of the coccyx together with the neoplasm.

the association between malignant clinical course and serum AFP-positivity. Other histologic patterns have been observed in malignant cases. Wilms' tumor of sacrococcygeal location was studied by light and electron microscopy in a 3 year old girl with a mass present since birth (Ward and Dehner). Neural tissue, cartilage, and glandular epithelia of respiratory and gastrointestinal types were only minor components of the tumor, 95 percent of which was composed of Wilms' tumor tissue. Obliteration of other tissues may have resulted in a dominant histologic pattern. The occurrence of extrarenal Wilms' tumor, presumably a teratomatous variant, was reviewed by Tebbi and associates. More information is needed concerning the morphology of the malignant component in cases with a clearly invasive course, or with obvious metastases. To state that any of the tissues forming a teratoma may undergo malignant transformation fails to convey the overwhelming predominance, in malignant cases, of a relatively small number of histologic patterns, particularly those showing neuroectodermal or yolk sac tumor differentiation (figs. 27–32). Furthermore, such an all-inclusive statement may be inaccurate, as the voluminous literature on sacrococcygeal teratomas contains no legitimate record of the presence of a number of sarcomatous patterns, most types of carcinoma, or typical trophoblastic malignancy.

In the first half of this century, the malignant part of these tumors was commonly referred to as "adenocarcinoma," "carcinoma," or "papillary adenocarcinoma," without further qualification

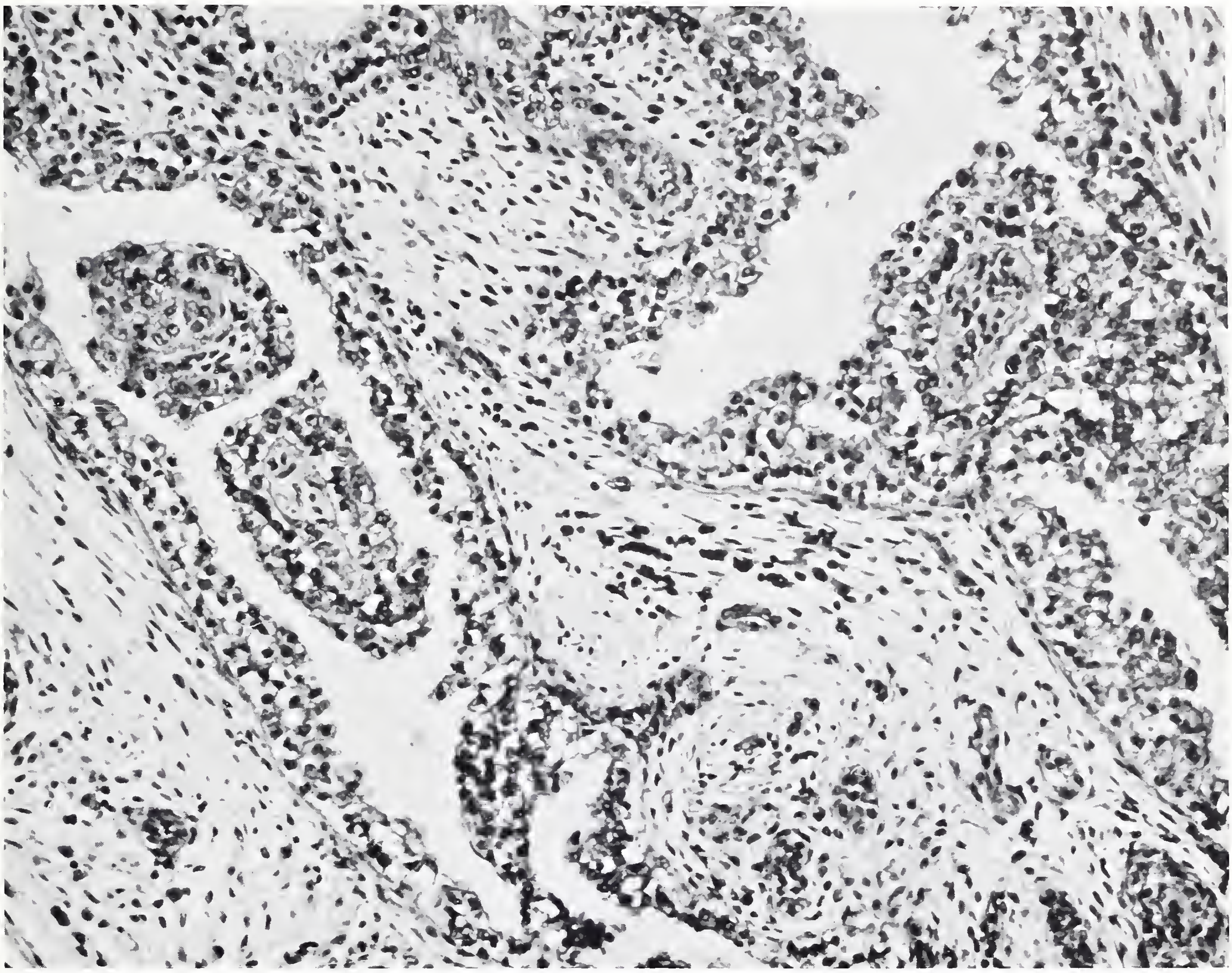

Figure 23
SACROCOCCYGEAL TERATOMA
Immature area of tubulo-alveolar glands lined by glycogen-rich epithelium lying in a myxoid stroma, reminiscent of fetal lung morphogenesis. X305.

(Lisco). The embryonic component of these teratomas may reproduce tubular structures, and sometimes this pattern predominates (figs. 29, 30); a transition to papillary formations may also be observed (fig. 31). These histologic appearances are apt to be confused with epithelial derivatives and indiscriminately named "adenocarcinoma." However, it is noteworthy that these appearances consistently develop in association with immature neuroectodermal tissue. Their resemblance to ependymal rosettes as seen in ependymomas and ependymoblastomas, or to the papillary structures of the same tumors, may be striking. Other so-called adenocarcinomatous areas may display malignant features, but critical review of published illustrations indicates that in many cases such areas could well fit into the spectrum of vitelline differentiation (figs. 33, 34). Conklin and Abell, subscribing to the germ cell theory of origin of teratomas, believed that the malignant histologic patterns observed in sacrococcygeal tumors are the same as those encountered in the gonads, except that neither germinoma nor choriocarcinoma are encountered. Chretien and associates studied 21 malignant sacrococcygeal tumors and used the name "embryonal adenocarcinoma" for the histologic pattern displaying malignant features. The criteria of malignancy in the latter two studies were infiltration of normal structures and presence of distant metastases. These reports called attention to the high frequency with which the malignant tumors arising in sacrococcygeal teratoma display a common histologic appearance reminiscent of "germ cell tumor," and established that the prognosis is always grave in such cases. In contrast, the presence of other immature tissues in the tumor parenchyma may or may not imply a malignant clinical course. In our experience, a pattern of tubular formations mimicking the embryonic neural tube may be malignant, but foci of myxoid, immature mesenchymal tissue, immature neural tissue, fetal muscle, nephrogenic tissue, etc., do not necessarily portend an adverse prognosis (figs. 23–25). The influence of tumor histology on prognosis is further discussed in the section on Prognosis.

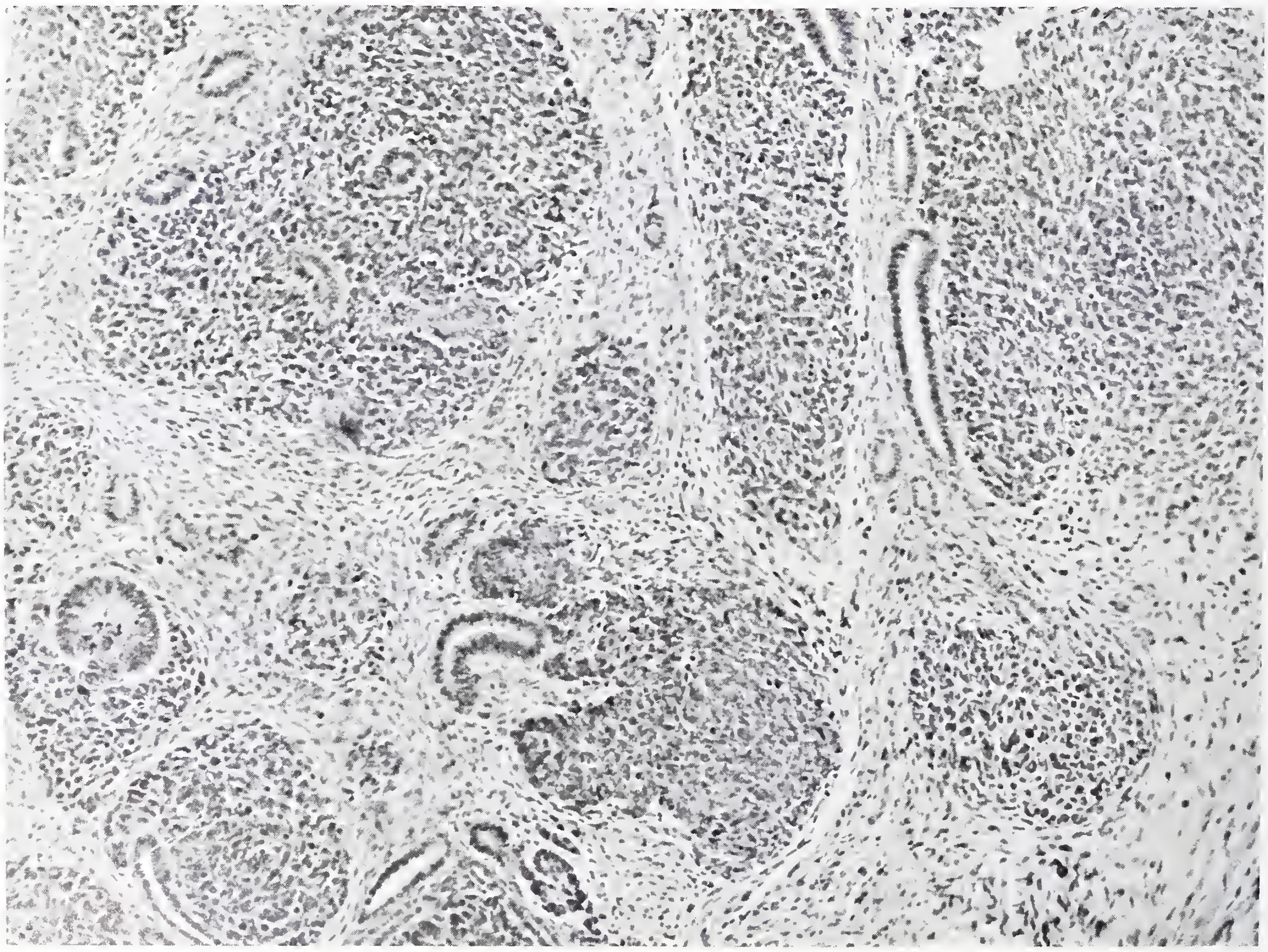

Figure 24
SACROCOCCYGEAL TERATOMA
Embryonic-appearing dark cells with the histologic arrangement of metanephrogenic blastema during embryonic nephrogenesis. This tumor recurred once, but the recurrence was entirely composed of mature tissues. X75. (From Gonzalez-Crussi, F., Winkler, R.F., and Mirkin, D.L. Sacrococcygeal teratomas in infants and children. Arch. Pathol. Lab. Med. 102:420-425, 1978.)

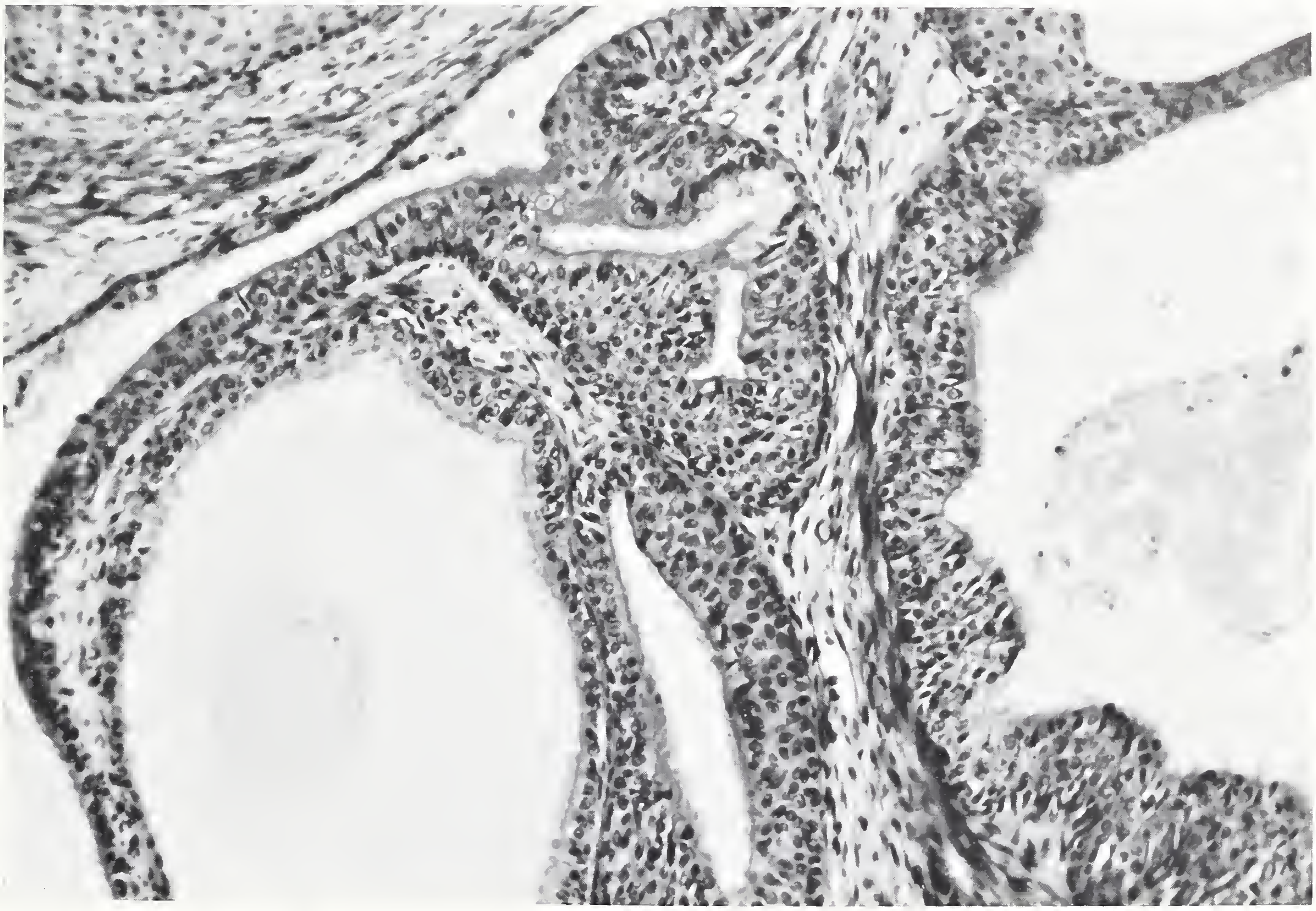

Figure 25
SACROCOCCYGEAL TERATOMA
Multicystic area in benign sacrococcygeal teratoma. A variety of epithelia are seen lining the cystic cavities. X225.

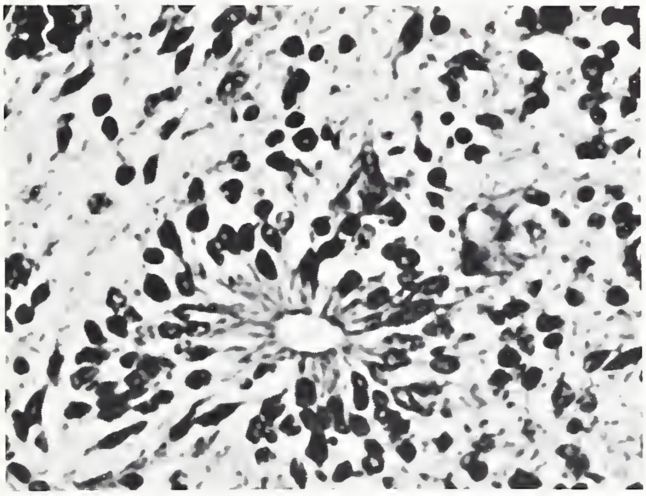

Figure 26
SACROCOCCYGEAL TERATOMA
Primitive neuroectodermal component in a clinically benign sacrococcygeal teratoma. Ependymal-like rosette with a small central lumen in a myxoid background. This tissue has an uncertain prognosis. The possibility of spread increases proportionally to its amount within the tumor. X400.

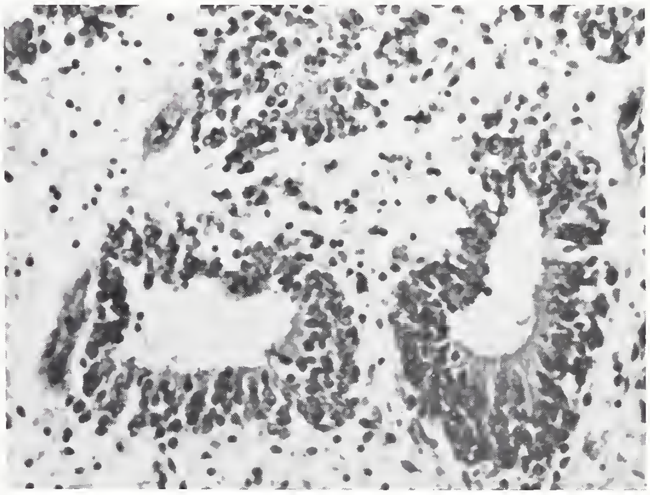

Figure 27
SACROCOCCYGEAL TERATOMA
Neuroectodermal component of a malignant sacrococcygeal teratoma, mimicking ependymoblastoma. Dark cells aggregate in dense clusters or form multilayered rosettes. X510.

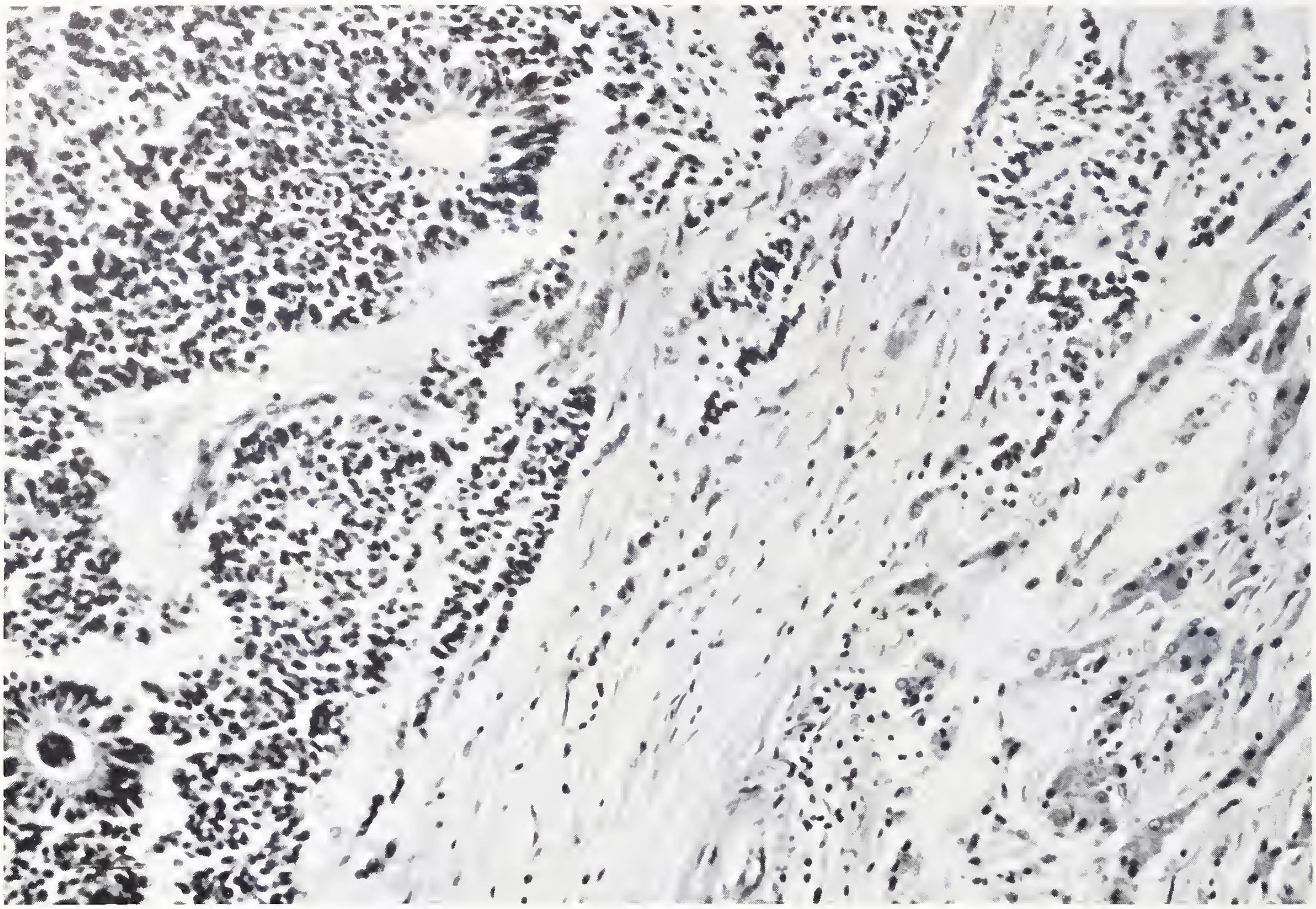

Figure 28
SACROCOCCYGEAL TERATOMA
Rosette-forming neuroectodermal cells metastatic to the liver. Parenchymal liver-cell cords appear compressed by the expanding metastatic nodule. X120. (From Gonzalez-Crussi, F., Winkler, R.F., and Mirkin, D.L. Sacrococcygeal teratomas in infants and children. Arch. Pathol. Lab. Med. 102:420-425, 1978.)

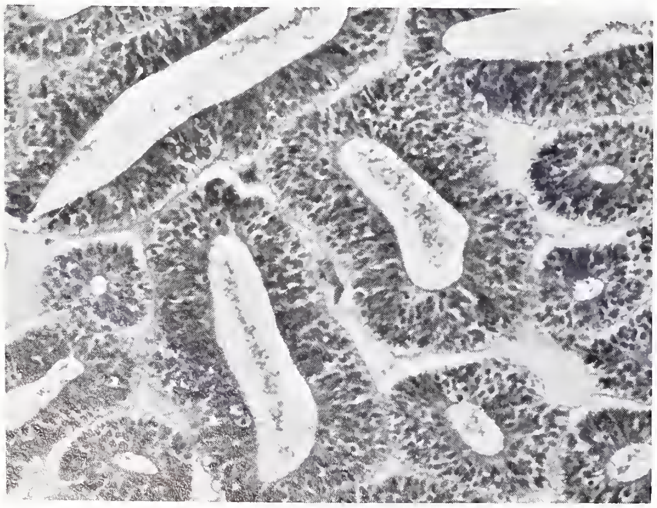

Figure 29
SACROCOCCYGEAL TERATOMA
Neuroectodermal component of sacrococcygeal teratoma, adopting a multitubular organoid pattern, often misnamed "adenocarcinoma." X175.

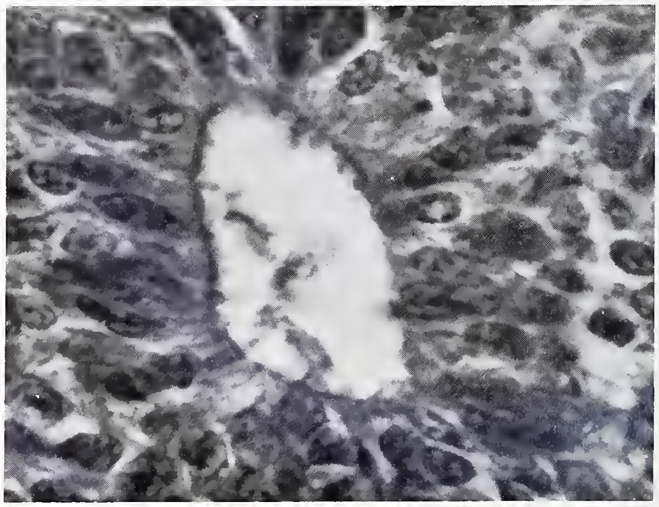

Figure 30
SACROCOCCYGEAL TERATOMA
High magnification of tubular area showing resemblance to the rosette-like arrangement seen in ependymomas. X610.

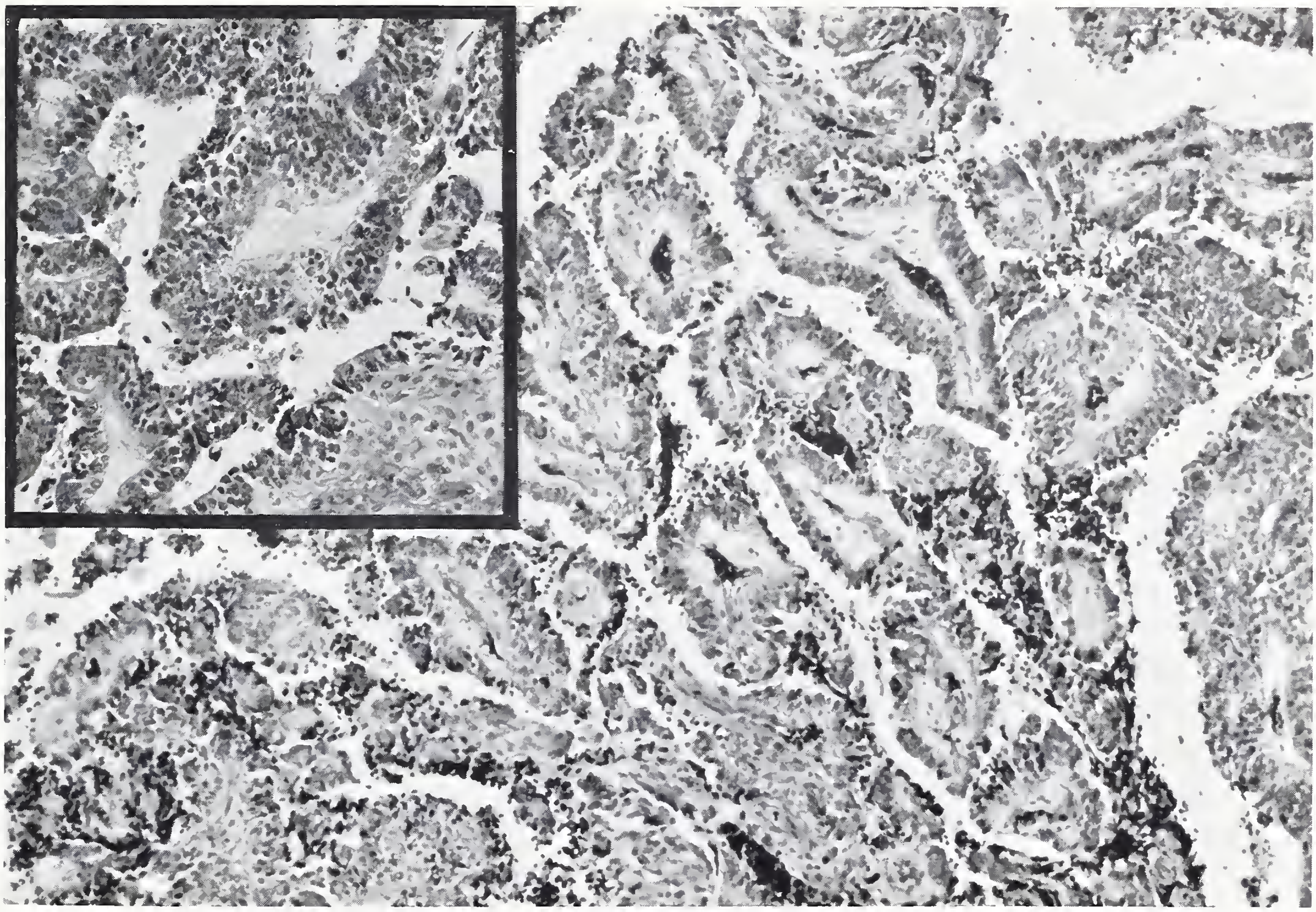

Figure 31
SACROCOCCYGEAL TERATOMA
Papillary configuration in a malignant area of sacrococcygeal teratoma. X175. Inset: Multistratified epithelium. X210.

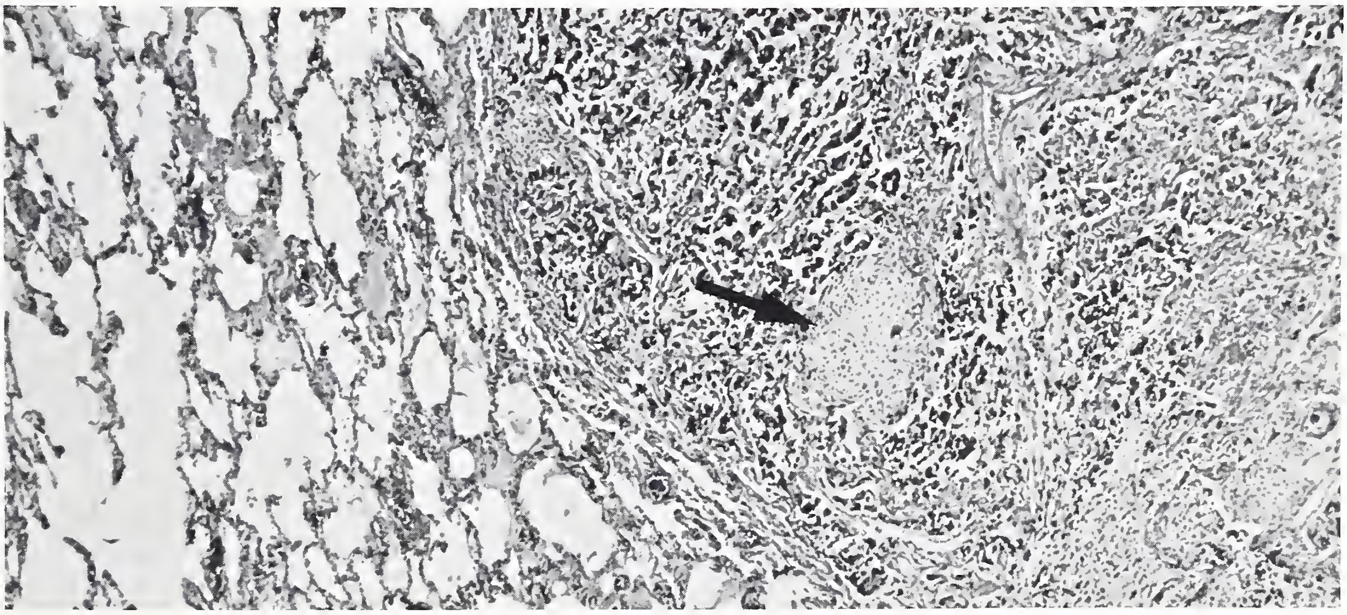

Figure 32
SACROCOCCYGEAL TERATOMA
Malignant sacrococcygeal teratoma metastatic to lungs. The tumor tissue is composed of embryonic neural tubules and primitive mesenchyme with foci of cartilagenous differentiation (arrow). X65.

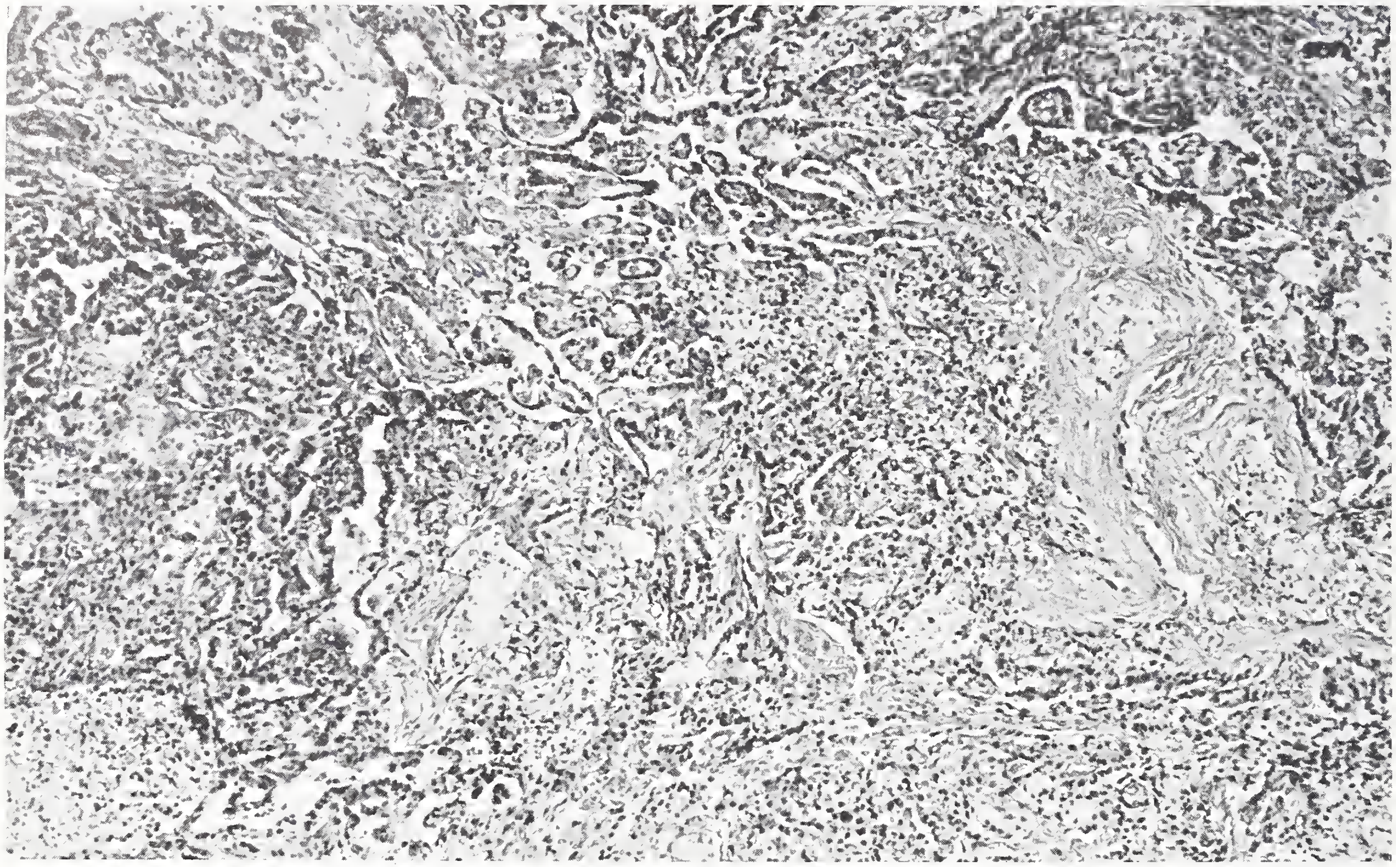

Figure 33
SACROCOCCYGEAL TERATOMA
Reticular and papillary histologic pattern characteristic of endodermal sinus tumor (yolk sac carcinoma) in a malignant sacrococcygeal teratoma. X80.

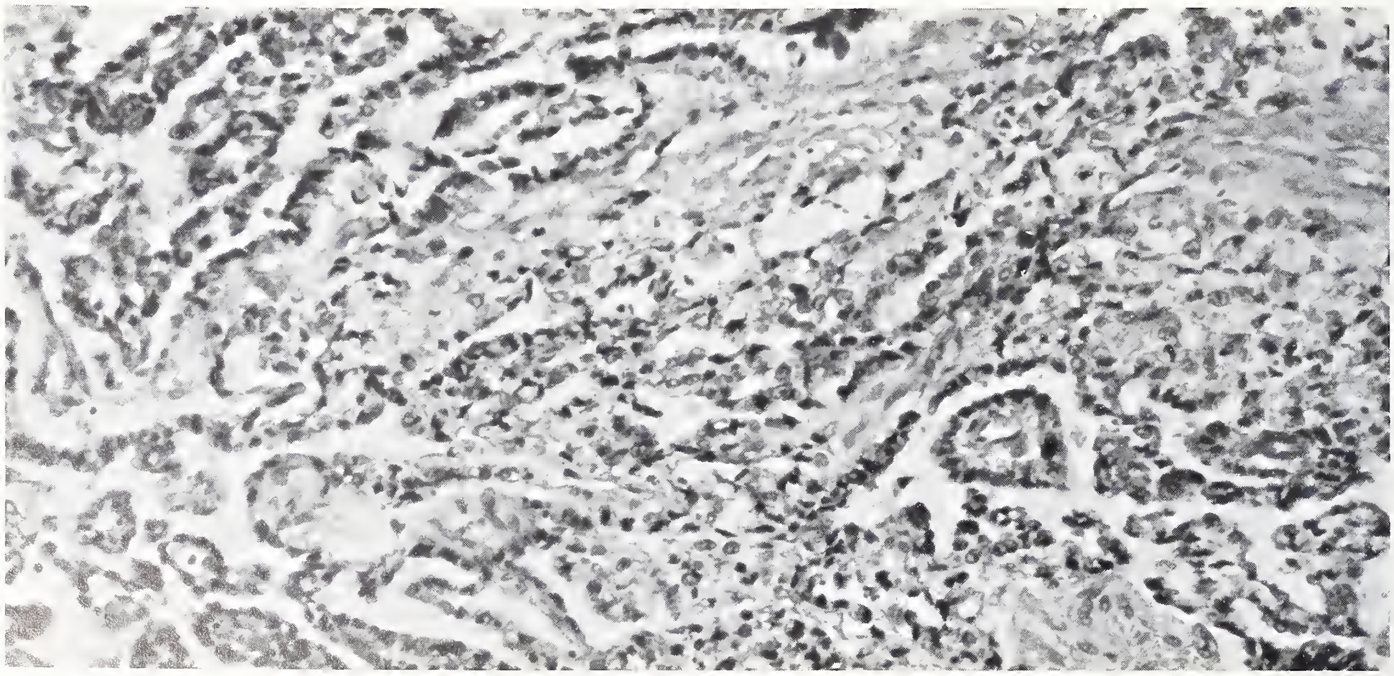

Figure 34
SACROCOCCYGEAL TERATOMA
Multiple delicate papillae in endodermal sinus tumor area of metastatic sacrococcygeal teratoma. The pulmonary metastatic deposits were entirely composed of tissue with the morphology of yolk sac carcinoma. X210.

Differential Diagnosis. In infants with sacrococcygeal teratoma, the most frequent clinical diagnostic error is confusion with myelomeningocele (Altman et al.). Other mistaken diagnoses made on initial examination are rectal abscess, lipoma, duplications, perineal cyst, lymphangioma, bladder neck obstruction, rectal prolapse, and congenital rectal stenosis. A consequence of an erroneous diagnosis is delay in implementing therapy. This is unfortunate, because the prognosis of lesions diagnosed and treated beyond the neonatal period is worse than that of tumors treated early in life. It should be remembered that meningoceles are nearly always cystic, and that a communication with the subarachnoid space may be suspected when compression of the cystic mass elicits ballooning of the fontanelles (Chaffin), or when the mass distends when the child cries, coughs, or strains (Crockford et al.). In contrast with meningocele, a sacrococcygeal teratoma will only exceptionally be shown to communicate with the subarachnoid space. Likewise, serious neurologic deficit does not ordinarily accompany a teratoma; sphincteric control and nervous function of the limbs are usually normal (Willox and MacKenzie). Roentgenologic examination may contribute to establish more firmly the distinction between these two conditions in ambiguous cases.

In adult patients, sacrococcygeal teratomas must be distinguished from pilonidal cysts, perirectal abscesses, fistulous tracts, and other inflammatory conditions of the lower intestinal tract. As all these conditions are much more common than the tumor under discussion, it is not surprising that teratomas should be often missed clinically. Thus, sacrococcygeal teratomas that manifest in adults have been treated for a long time as perirectal fistulas (Haidak and Bates) or other diseases before it was realized that a tumor was responsible for the symptoms.

After the tumor tissue has been examined histopathologically, diagnostic doubts should be dispelled. However, nonteratomatous lesions of mixed tissue composition may occur in the spine, which may be the source of confusion. Masses entirely made up of benign mesodermal derivatives and presenting on the thoracolumbar region along the midline have been called "midline hamartomas" (Tibbs et al.) and purported to represent a clinicopathologic entity. These lesions may produce widening of the spinal canal, but behave in a benign fashion; additional observations are required to determine their taxonomic place. They contain neither epithelial nor cystic elements, and this feature should facilitate their distinction from teratomas.

Prognosis. The most important prognostic determinants are: age at diagnosis; extent of disease when the tumor is discovered; nature of the neoplastic tissue components; amount of immature elements; and presence of complications or associated conditions.

Age has a dramatic influence on prognosis. In the series of Donnellan and Swenson, when the teratomas were discovered between birth and two months of age, 10 percent (8 of 71) were malignant; however, of teratomas discovered after two months of age, 91 percent (22 of 24) were malignant. In that series, malignancy was defined by presence of actual invasion or metastases, and not purely on the presence of histologically immature tissues. Virtually all published series agree on the fact that with increasing age beyond the newborn period, the incidence of malignancy clearly increases several fold. Whether neoplastic tissues present since birth undergo a sudden growth spurt, or whether de novo inception beyond the neonatal period is associated with greater risk of malignancy, is not known. In either case, the main cause of death in these infants is malignancy (Hickey and Layton; Hunt et al.); therefore, no possible justification exists for a contemporizing attitude. The survey of the American Academy of Pediatrics lent support to the contention that the tendency for malignancy is greater in males: incidence of malignancy before two months of age was 7 percent in females and 10 percent in males; after two months, it was 48 percent in females and 67 percent in males (Altman et al.). Thus, although sacrococcygeal teratoma is more common in females, and although malignancy may supervene regardless of the patient's sex, males are distinctly at a disadvantage in this regard.

Of the 24 cases collected by Miles and Stewart in adult patients, only two were malignant. A low incidence of malignancy has been found in adults with sacrococcygeal teratoma (Leslie et al.; Mears; Miles and Stewart), in apparent contradiction with the statement that the longer a teratoma is allowed to remain in its host, the higher the likelihood of malignant course. This apparent discrepancy has produced some bewilderment (Pantoja and Rodriguez-Ibañez) and uncertainty about the true incidence of malignancy in sacrococcygeal teratoma. A way to reconcile these seemingly opposing data is to acknowledge that a high proportion of all the congenital sacrococcygeal teratomas, around 25 percent, are definitely malignant, and are lethal to their hosts in a very short time, i.e., during infancy or childhood. The patients who survive to adult age manage to do so because, in all likelihood, they harbor tumors endowed with comparatively limited capacity for proliferation and low malignant potential. Thus, their tumors progress slowly and manifest clinically in later years. Alternatively, it may be proposed that large tumors that manifest at birth are more likely to be benign, whereas at least some sacrococcygeal teratomas may originate in later years, and these may be malignant from their inception. Be that as it may, a long period of dormancy may be suddenly interrupted by malignant transformation. As inferred from the series quoted here, the risk of this transformation may be as high as 10 percent or greater. Hence, a conservative or expectant attitude is justified in the treatment of neither adult nor infantile forms of sacrococcygeal teratoma.

The term "malignant" has been used too liberally in the past to designate teratomas containing foci of immature cells. As stated previously, a high rate of recurrence and early development of metastasis may be anticipated when foci of yolk sac carcinoma are discovered in the tumor, but immature somatic tissues do not necessarily signify a malignant prognosis. Lisco considered the reports of "chondrosarcoma" or other mesenchymal malignancies insufficiently documented in sacrococcygeal teratoma.

Metanephrogenic embryonic tissue with the appearance of Wilms' tumor has been regarded as malignant and treated accordingly (Ward and Dehner), but evidence of metastatic involvement has not been provided. Small foci of metanephrogenic tissue have been observed in teratomas that did not metastasize (Gonzalez-Crussi et al.). On the other hand, complacence would be unjustified upon discovering abundant areas of nongerminal immature tissues. Immature neuroectodermal tissues are among the most common types of tissue encountered in sacrococcygeal teratoma. Rarely, they can metastasize (Gonzalez-Crussi et al.), although the finding of progressively maturing glial islands in successively recurrent teratomas may indicate a tendency toward advancing differentiation. Information is scanty on the proclivity for distant dissemination and infiltrative potential of the various somatic or nongerminal tissues. Although this occurrence must be very rare, it seems prudent to carefully monitor all patients whose teratomas contain very abundant amounts of immature, or incompletely differentiated tissues. No objective criteria exist for quantification of such tissues, but a rough estimate may be derived from examination of at least one randomly obtained tissue section per centimeter of the largest diameter of the tumor.

Argentaffin carcinoma of the sacrococcygeal region, verified by electron microscopy, has been diagnosed (Aparicio et al.) in an adult patient without postoperative evidence of excess tryptophan metabolites in the urine. No metastases were present, and the ultrastructural and histochemical features of the secretory granules were compatible with carcinoid of hindgut origin. Mention is made of hypernephroma of the sacrococcygeal region (Gwinn et al.), which, like Wilms' tumor of the same area (Ward and Dehner), may have a teratomatous origin, or perhaps takes origin from ectopic metanephrogenic remnants of the type described by Gruenwald in a 20 mm. human embryo with myeloschisis.

Marcuse reported a sacrococcygeal teratoma in an adult that gave rise to rapid metastases, and was associated with a positive frog test for pregnancy. The microscopic description cautiously notes a "resemblance to choriocarcinoma" and the illustrations show syncytial giant cells. This remains the only observation of a possible choriocarcinoma component. All these observations constitute rarities, and do not invalidate the general conclusions enunciated above.

The presence of associated conditions requires no further comment. The prognosis and treatment depend upon the nature of the associated disease. The single most common complication leading to death after attempted surgical extirpation has been hemorrhage (Smith et al.). This led to advocacy of early ligation of middle sacral vessels during surgery for these tumors.

Treatment. The treatment of choice for these tumors is immediate removal. Despite the formidable appearance of many of these lesions, they are quite amenable to early surgical intervention. The newborn infant tolerates the procedure well (Willox and MacKenzie) in the absence of serious complications, and the size of the growth is no contraindication to standard surgical therapy. Because the volume of many of the large cystic tumors regresses dramatically once the fluid is evacuated from the cystic cavities, puncture and drainage were performed in the past; a large teratoma devoid of fluid contents may shrink dramatically to small flaps of skin compatible with normal activities. As primary treatment, such a procedure is definitely contraindicated today, given the high risk of malignant transformation in the unexcised tumors. Nonetheless, incision and drainage may have to be performed as a measure preliminary to definitive surgery, in the rare cases in which a previously undiagnosed sacrococcygeal tumor interferes with delivery of an affected infant during parturition. An intravaginally performed incision resulted in the delivery of a liveborn baby that might have succumbed otherwise (Weiss et al.).

In the common form of teratoma with predominantly external growth (Type I), the surgical approach most generally advocated is a posterior one, with the patient in the prone position. The coccyx is routinely removed en bloc with the tumor, and should be properly identified in the specimen. Some teratomas are strikingly pedunculated large masses, joined to the coccyx by a narrow fibrous pedicle. In the past, it seemed relatively simple to amputate these tumors from the pedicle, away from the coccyx, with a minimum of operative morbidity. This practice has been completely abandoned since it was realized that the recurrence rate is significantly decreased by complete excision of the coccyx together with the tumor (Pantoja and Rodriguez-Ibañez; fig. 22). In 1951, Gross and associates reported a recurrence rate of 35 percent for pedunculated tumors treated by simple excision; however, when the coccyx is incorporated in the specimen, and there is verification of complete surgical ablation by histopathologic examination, the odds of recurrence in a well differentiated teratoma are virtually nil (Graham and McKenzie). Ligation of the middle sacral artery and vein to ensure hemostasis should be an early step of the operation, preceding teratoma manipulation (Chretien et al.).

Tumors with dumbbell extension into the pelvis, when massive, pose special surgical problems. Some of these tumors cannot be removed by the usual posterior approach. Combined anterior and posterior excision, either as a single or multiple-stage procedure (Priebe), may be required. Izant reported 33 percent overall mortality. This author combined the data of four published series and concluded that fatalities due to recurrence of histologically benign tumor tissue doubled in patients operated on after one month of age, and the mortality due to recurrence of histologically malignant tissue increased fivefold after the same age, thus stressing the importance of early treatment.

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◆

TERATOMAS OF THE MEDIASTINUM (EXTRAPERICARDIAL)

Of 1064 exploratory thoractomies performed at the Mayo Clinic from 1929 to 1968 for the diagnosis and treatment of mediastinal masses, 99 (9.3 percent) resulted in a diagnosis of teratoma; the mediastinum was thus found to be second only to the gonads as a primary location of teratomas in adults. (Wychulis et al.). The incidence of mediastinal tumors among all hospital admissions has been calculated at approximately 1:3400 (Daniel et al.; Sabiston and Scott). A strong female predominance has been seen in one series (Bergh et al.) of benign teratomas, whereas males have predominated in other series (Ringertz and Lidholm; Rusby; Wychulis et al.). Males clearly predominate when only malignant teratomas are considered. The most common location is the anterosuperior mediastinum. Although some of these tumors may be congenital, the diagnosis is often made in adolescents or young adults. Correspondingly, case series of teratomas comprising children only fail to show a high frequency of primary mediastinal involvement. Thus, depending on the nature of the population from which the case material is drawn, a mediastinal location has been observed in between 4.7 percent (Galy) and 27 percent of all teratomas.

No definite etiologic factors are known. Genetic influences may be operative in some cases, but this is speculative. A case report of involvement of two nontwin brothers with mediastinal germ cell tumor supports the role of genetic factors (Jayet et al.). Curiously, these two patients were diagnosed at the same age (26 years), a year apart; one had a tumor composed of teratomatous tissues with areas of embryonal carcinoma, the other a choriocarcinoma. Only in the latter patient was a testicular tumor excluded by histologic examination of the testes at autopsy. A relationship between embryopathy and teratoma is also suggested by the association of chromosomal abnormality and mediastinal teratoma. A patient with XXY Klinefelter's syndrome, Fallot's "trilogy," precocious puberty, and mediastinal teratoma, was described by Pierson and associates. Follicle stimulating hormone (FSH) was secreted by the tumor; the abnormal hormone and the manifestations of precocious puberty regressed after ablation of the tumor.

Clinical Features. Mediastinal tumors in general tend to produce symptoms and signs due to compression or actual invasion of important structures found in this anatomic area. The most common symptoms are cough, dyspnea, and chest pain, but it is important to emphasize that half the children bearing a mediastinal tumor may be asymptomatic (Whittaker and Lynn). Voluminous teratomas are prone to compress adjacent bronchi and lung parenchyma, thus giving rise to symptoms. Secondarily, the lung may become infected and infection may spread to the teratoma either hematogenously or via communicating bronchi. When a teratoma perforates into the lung or the airway, the patient may expectorate hair (trichoptysis) or keratinous material. This is an uncommon occurrence, but one which is diagnostic of the nature of the tumor. Discharge of the contents of cystic tumors into the lungs and the bronchial tree may lead to lipoid pneumonia, a serious complication, albeit one that is seen with less frequency as the treatment of these tumors becomes more opportune. Acute manifestations and effusion into the pleural cavity may herald rupture of the mediastinal tumor into the pleural space (Bothra et al.). Pneumothorax has been known to constitute a baffling manner of presentation of mediastinal teratomas (Singh et al.). Acute exsanguination may be due to perforation of the tumor into great vessels. Acute cardiac tamponade may be due to perforation into the pericardial sac (Thompson and Moore; Yusoff).

A chronic syndrome of "acquired pulmonary stenosis" has been known to develop as a result of gradual compression of the pulmonary artery by the expanding tumor (Littler et al.). In most cases, the tumor responsible is a teratoma (Flammang et al.; Fry et al.; Gough et al.; Littler et al.; Maier; Rusby), but other tumors of this area may produce the same clinical syndrome (Flammang et al.). This syndrome is characterized clinically by a pulmonary murmur that may disappear at the end of inspiration and intensify at the end of expiration; a parahilar mass on x-ray; normal electrocardiogram or features indicative of right ventricular hypertrophy; and normal or high pulmonary systolic gradients on cardiac catheterization. Of 20 cases reviewed by Flammang and associates, the outcome was favorable in 10; their own case was a malignant teratoma with multiple metastases found at autopsy.

Some cases of mediastinal teratoma have caused compression or destruction of nervous system structures. Horner's syndrome, signs and symptoms of spinal cord compression, intercostal nerve neuralgia, or dysphagia may be encountered. Other patients may manifest a full-blown syndrome of superior vena cava obstruction. None of these clinical presentations offers any reliable assistance in distinguishing benign from malignant teratomas, although pronounced weight loss and signs of compression are more common in patients bearing a malignant tumor (Adebonojo and Nicola).

In the newborn infant, an extrapericardial anterior mediastinal mass is only rarely the cause of severe respiratory distress, but a few cases have been reported (Adler et al.; Hagopian and Johnson; Pate et al.). In patients with teratomas manifesting shortly after birth, the tumor did not present as a midline mass, but projected predominantly toward the left hemithorax. In older children, the tumors that cause respiratory symptoms have often been eccentric, without left-sided preference (Stechmiller et al.). On occasion, the extensions of a teratoma into the pulmonary parenchyma may be inseparable from the lung tissue, perhaps as a result of prolonged inflammatory reaction, as may occur from rupture of a cyst (Maier). The diminutive size of the superior mediastinum in a small infant determines the ease with which a critically placed neoplasm interferes with normal ventilation and causes compression of vital structures. Symptomatic mediastinal tumors in infants are potentially lethal; serious consequences result when thoracotomy is delayed. A mediastinal teratoma was present in a 28-week stillborn fetus with hydrops fetalis of unknown origin (Macafee et al.), suggesting that there may also be serious systemic effects in prenatal life.

Mediastinal teratomas may exhibit endocrine secretory activity. Asymptomatic hypoglycemia and elevated plasma levels of immunoreactive insulin were observed in a 5 year old boy with a mediastinal teratoma

(Honicky and de Papp). These values returned to normal after removal of a tumor that contained abundant pancreatic endocrine tissue. This patient also had elevated serum levels of growth hormone and cortisol preoperatively, which were explained as phenomena tending to promote gluconeogenesis and to antagonize insulin effects. Secretion of HCG and androgenic substances resulting in sexual precocity has also occurred. The mediastinal teratomas in such cases were either of the immature "polyembryoma" type, or were composed of both mature and immature tissues (Job et al.; Pierson et al.; Prieto Veiga et al.). Secretion of pancreatic enzymes from the tumor has been incriminated as a cause of inflammation and tumor disruption. Fistulous tracts might arise as a consequence of such enzymatic digestion (Sommerlad et al.) as well as following bacterial infection.

An atypical clinical presentation has been described in patients harboring mediastinal teratomas with a malignant germ cell component of embryonal carcinoma type. This clinical complex, called "the atypical teratoma syndrome" by Fox and associates, is observed in young men whose predominant symptoms and signs refer to metastatic disease in supraclavicular lymph nodes and lung with no apparent primary site. Biopsied lesions are commonly diagnosed as metastatic adenocarcinoma, and the primary site goes undiagnosed for some time. Eventually, investigation of serum tumor markers and review of the histology lead to a diagnosis of atypical germ cell tumor. The mediastinal origin of the primary tumor is subsequently recognized, after exclusion of the gonads as potential sites of a primary neoplasm.

Roentgenologic and Laboratory Examination. X-ray films of the chest in frontal and lateral projections usually reveal the mediastinal teratomas as sharply demarcated shadows that deform the mediastinum and project beyond the mediastinal boundaries into the adjacent lung fields (figs. 35–37). The majority are asymmetrically placed. As with other teratomas, the diagnosis may be made confidently when teeth or organized skeletal parts are seen within them. Calcification may be extensive (Ochsner; Paquet et al.). Otherwise, the radiographs by themselves are not diagnostic, and the radiologist resorts to the considerations discussed under Differential Diagnosis, in order to form an opinion. Mediastinal cystic hygromas, cysts of foregut origin, alimentary tract duplications, and a variety of benign and malignant neoplasms may be encountered within the mediastinum. All tend to appear as homogeneous globular shadows on roentgenologic examination (Caffey).

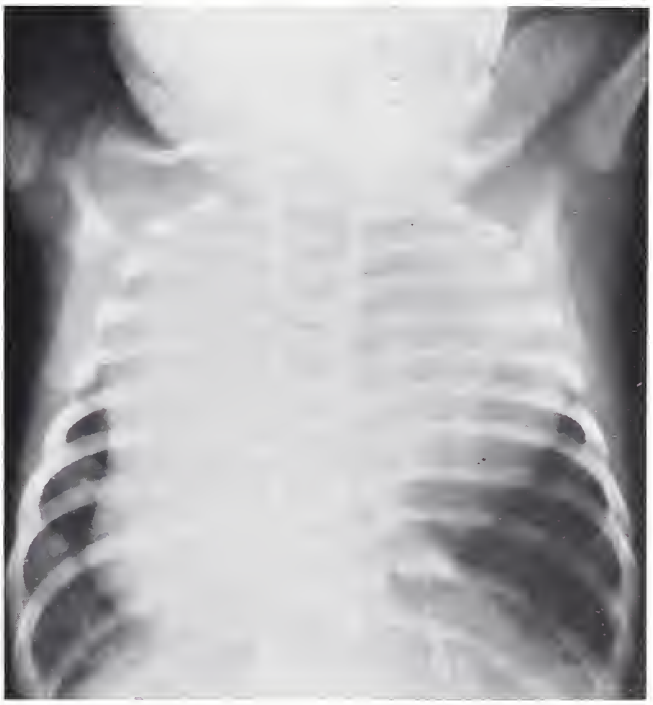


Figure 35
MEDIASTINAL TERATOMA
Symptomatic mediastinal teratoma in an infant, largely filling the right hemithorax. Anteroposterior view.

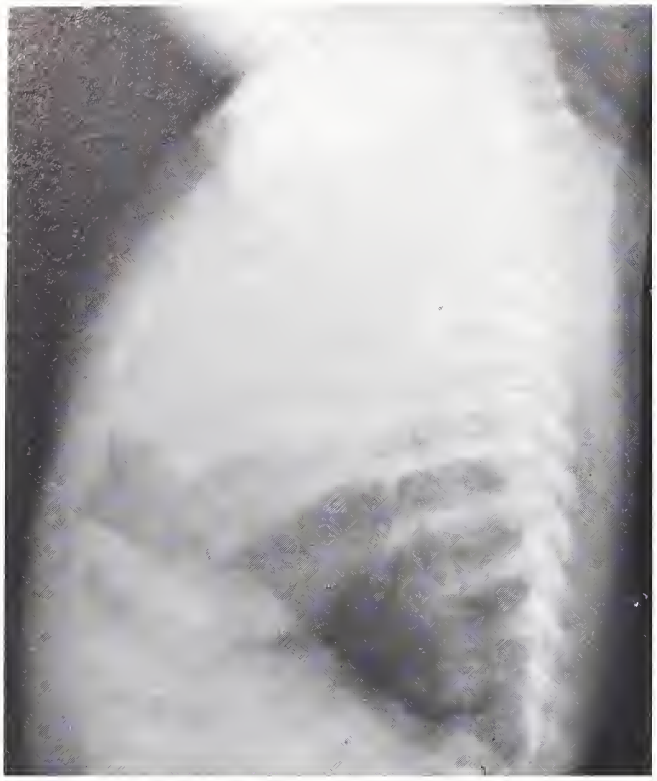


Figure 36
MEDIASTINAL TERATOMA
Lateral x-ray view of voluminous anterior mediastinal teratoma.

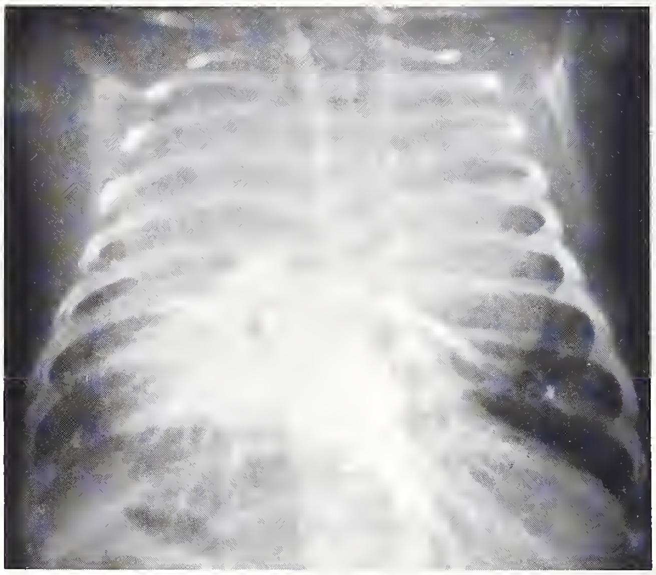


Figure 37
MEDIASTINAL TERATOMA
Angiocardiographic study in a 2 month old male infant, revealing severe displacement of cardiovascular structures by a teratoma. (Courtesy of Dr. E. Franken, Indianapolis, IN.)

The clinical laboratory may contribute with a variety of resources in the investigation of secretory products of the neoplastic tissues composing a teratoma. Alpha-1-fetoprotein determinations in the serum may be of value to establish the presence of a yolk sac tumor component. Endocrinologic syndromes may require the laboratory investigation of different hormonal compounds. Radioimmunochemical or other methods can identify the tumor-produced hormone; such identification should be attempted when appropriate technics are available. A recent observation has documented the presence of Klinefelter syndrome in a child with sexual precocity, mild testicular enlargement, and elevated HCG (2500 mIU per g. of tumor tissue were found) (Floret et al.). Only minimal dysmorphic changes were seen in the patient, but testicular biopsy changes of sclerosis and hyalinization were comparable to the findings in adult patients with this syndrome, and karyotyping showed an XXY chromosomal complement. It was suggested that this association may be more than fortuitous. The mediastinal tumor was a polyembryoma, which we consider a type of undifferentiated teratoma, as discussed in the section on Nomenclature. In another case, reported by Walden and co-workers, the urinary excretion of HCG (normal: 10-50 IU/L) was elevated to 1.4 x 10^3 IU/L in an 11 year old boy with acne and precocious development of secondary sexual characteristics. The patient had a mediastinal teratoma with trophoblastic elements.

Gross Appearance. Teratomas of the mediastinum are most commonly located in the anterior mediastinum at the base of the heart, in close relationship to the roots cf the great vessels. In a series of 106 cases, 82 benign and 18 malignant tumors projected mainly toward the left hemithorax from their origin in the mediastinum; 34 benign and 9 malignant tumors extended mainly to the right hemithorax, whereas only 6 benign tumors remained confined to the anterior mediastinum (Wychulis et al.). Benign tumors tend to be smooth and rounded, whereas malignant lesions, due to encroachment upon neighboring structures, are often of lobulated contour (Recondo and Libshitz); this difference may be useful radiologically, but its value is limited, since the large benign lesions also become lobulated due to extrinsic pressures. Massive growths may invade both hemithoraces, and the existence of two independent mediastinal teratomas, simultaneously growing to each side, is also recorded (Imes and Hook; Maier; fig. 38). Benign teratomas appear as encapsulated lesions that are usually multicystic, but on occasion may be predominantly solid (fig. 39). In the capsule, remnants of thymic tissue are frequently seen (Inada and Nakano, 1958, 1959; Ringertz and Lidholm; Schlumberger). The average diameter of the

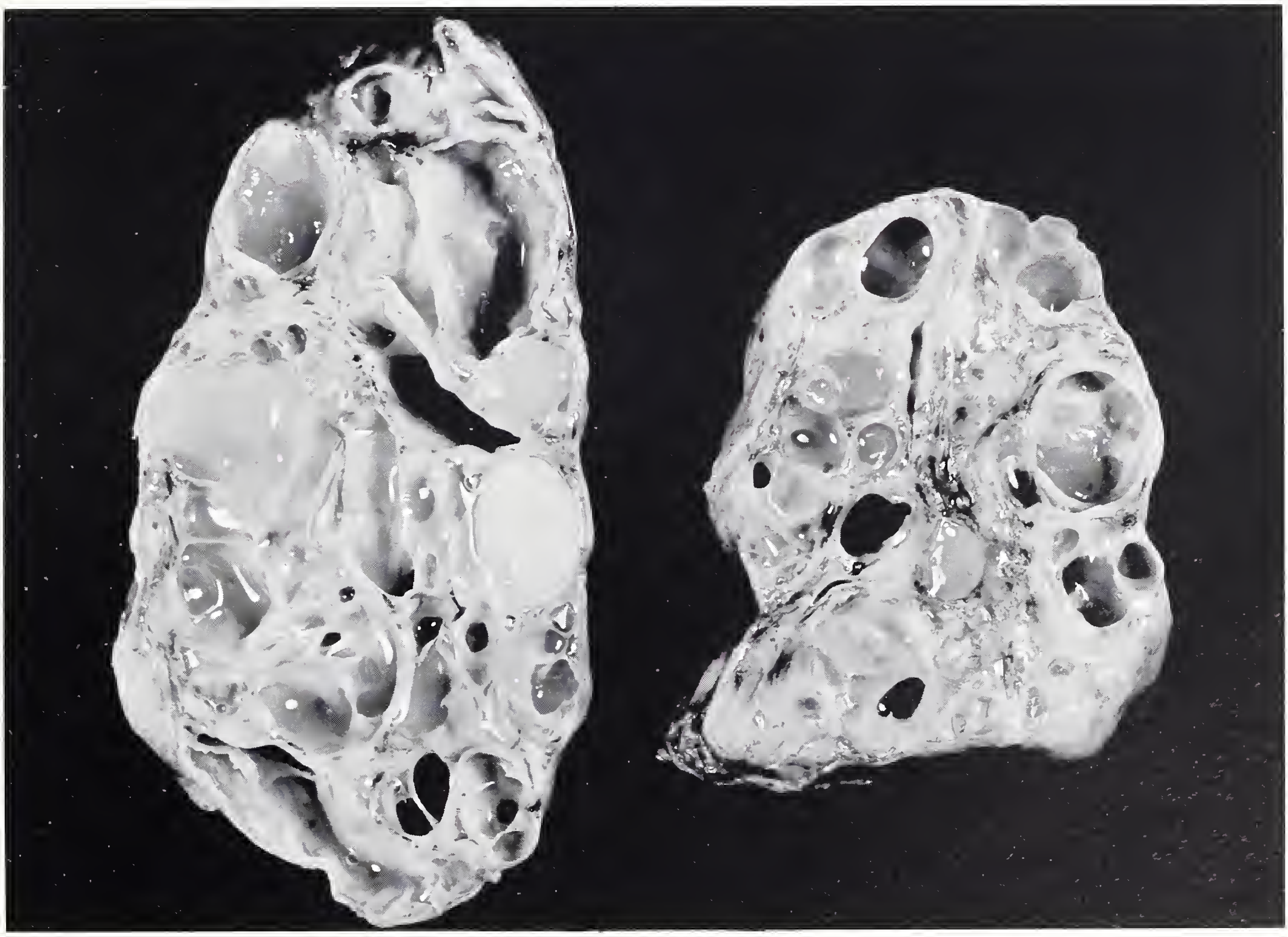


Figure 38
MEDIASTINAL TERATOMA
Cut surface of two mediastinal teratomas surgically removed from the same patient. Each tumor encroached upon the corresponding hemithorax. Multicystic gross appearance is characteristic of benign teratoma.

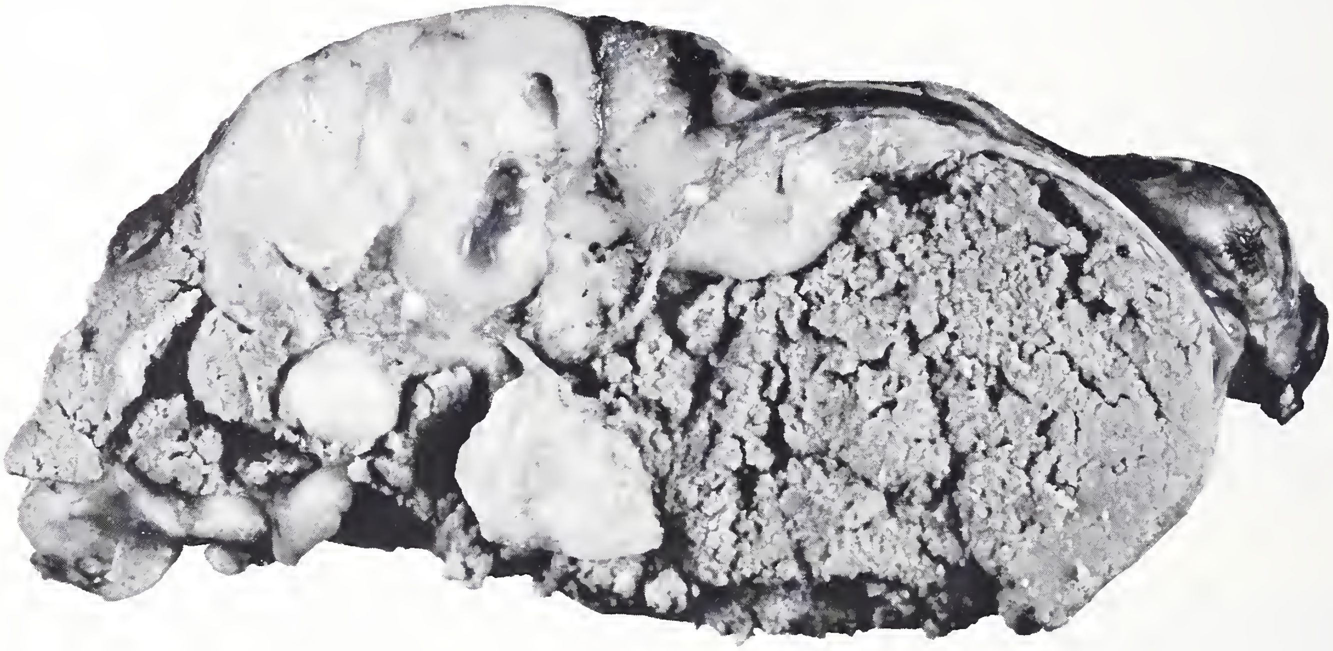


Figure 39
MEDIASTINAL TERATOMA
Variegated gross appearance of benign mediastinal teratoma removed from a 13 month old infant. (Courtesy of Dr. Frederick B. Askin, St. Louis, MO.)

surgical specimen is around 10 cm. The cystic cavities are occupied by clear, yellow or brown fluid, and often by sebum or hair. Papillary structures may be seen projecting into the lumen of the cysts. Teeth are not uncommonly apparent within the tumor (Blades).

Microscopic Appearance. Benign mediastinal teratomas usually display a number of cystic structures lined by mucus-producing, tall epithelium. A large amount of tissues of different nature are encountered, often with marked tendency to organ formation (pl. II; figs. 40, 41). Bronchial and foregut-derived structures were present in only 15 of 186 mediastinal tumors reviewed by Diaconitza and Eskenasy, whereas pancreatic tissue was present in only 3 cases of this series, separately reported by Nicolesco and associates (1971, 1972). These observations are at variance with most reported series, in which endodermal structures, including pancreas, are a very common component of mediastinal teratomas. The importance of the presence of pancreatic tissue in mediastinal teratomas relates in part to a possible hormonal secretion from islet cells, and in part to enzymatic acinar secretion, which may lead to necrosis, inflammation, and acute clinical manifestations (Nicolesco et al., 1971, 1972; Sommerlad et al.). Thymic tissue is often found around the periphery of mediastinal teratomas (Schlumberger). Inada and Nakano (1958) found this tissue in 11 of 15 specimens, whereas pancreas was present in 6. Skin and its appendages and cystic structures lined by squamous epithelium are among the most common tissues encountered.

Malignant mediastinal teratomas are usually included in reviews of germ cell

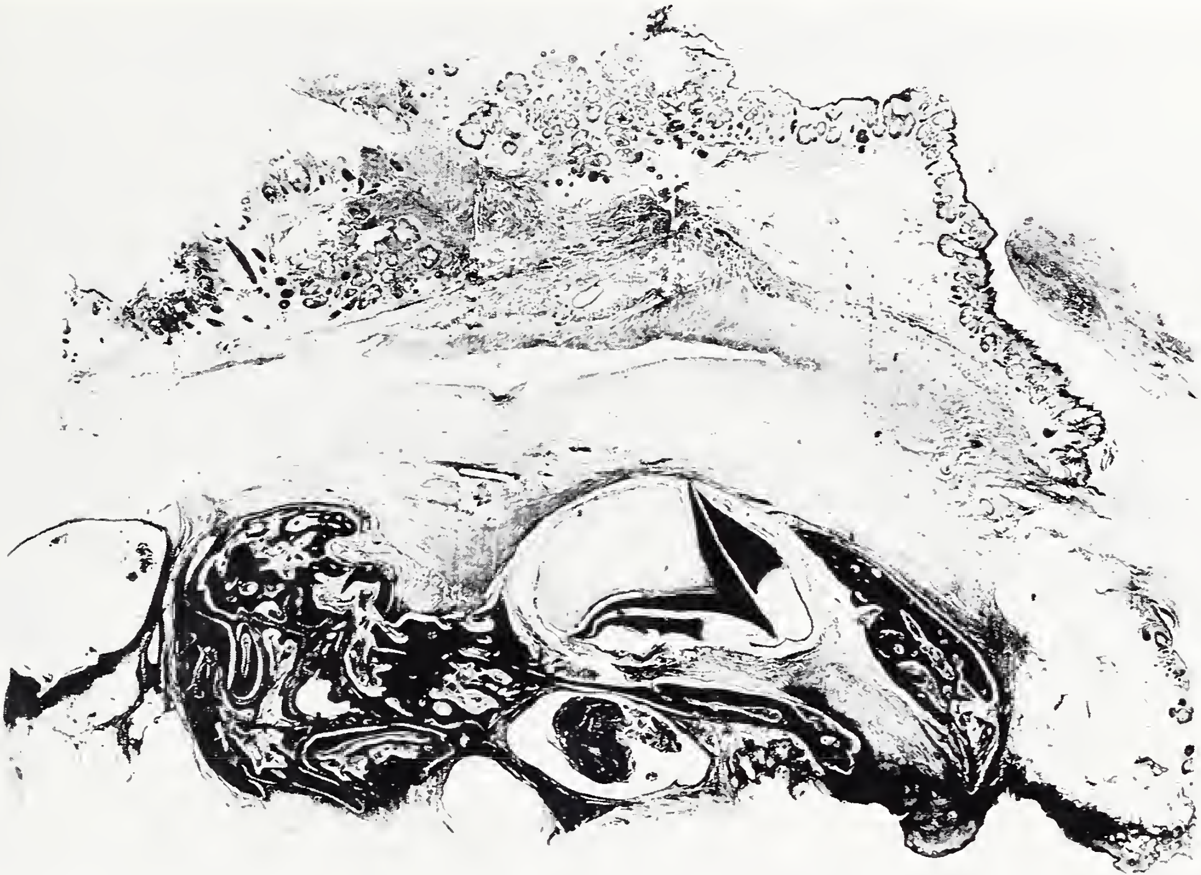


Figure 40
(Figures 40 and 41 from same case)
MEDIASTINAL TERATOMA
Section of tooth-containing part of the teratoma. X5. (Also fig. 13, Fascicle 9, First Series, Teratomas. Atlas of Tumor Pathology.)

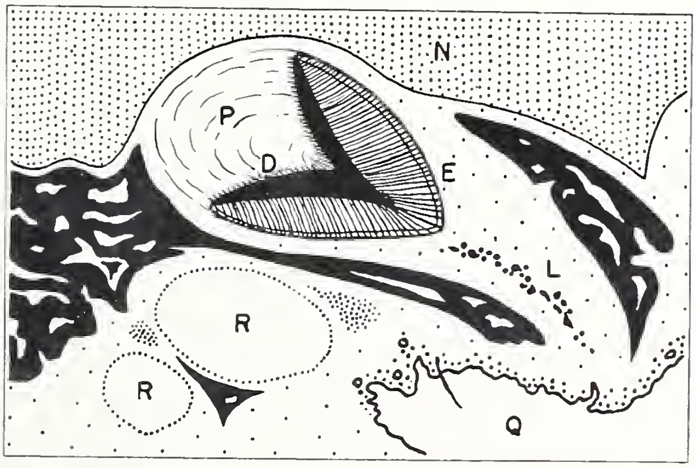


Figure 41
MEDIASTINAL TERATOMA
Diagram of components of part of the teratoma illustrated in the preceding figure. (R) respiratory cavities; (Q) skin cavity; (P) dental pulp; (D) dentin epithelium; (E) enamel; (L) dental lamina; (N) central nervous tissues. (Also fig. 14, Fascicle 9, First Series, Teratomas. Atlas of Tumor Pathology.)

tumors of extragonadal origin. Unfortunately, the term "malignant teratoma" or "teratocarcinoma" has been used to designate a number of structurally different germ cell tumors, whether of "pure" histologic type, such as seminoma or choriocarcinoma, or of combined histologic type and with or without well differentiated somatic tissues present in the tumor. A consequence of this imprecision has been that clinical discussions of malignant mediastinal teratomas deal with a heterogeneous group of tumors, and clinicopathologic correlations are correspondingly difficult to establish. There are conceptual reasons to consider germ cell tumors as subclasses of teratomas. Such hypothetical

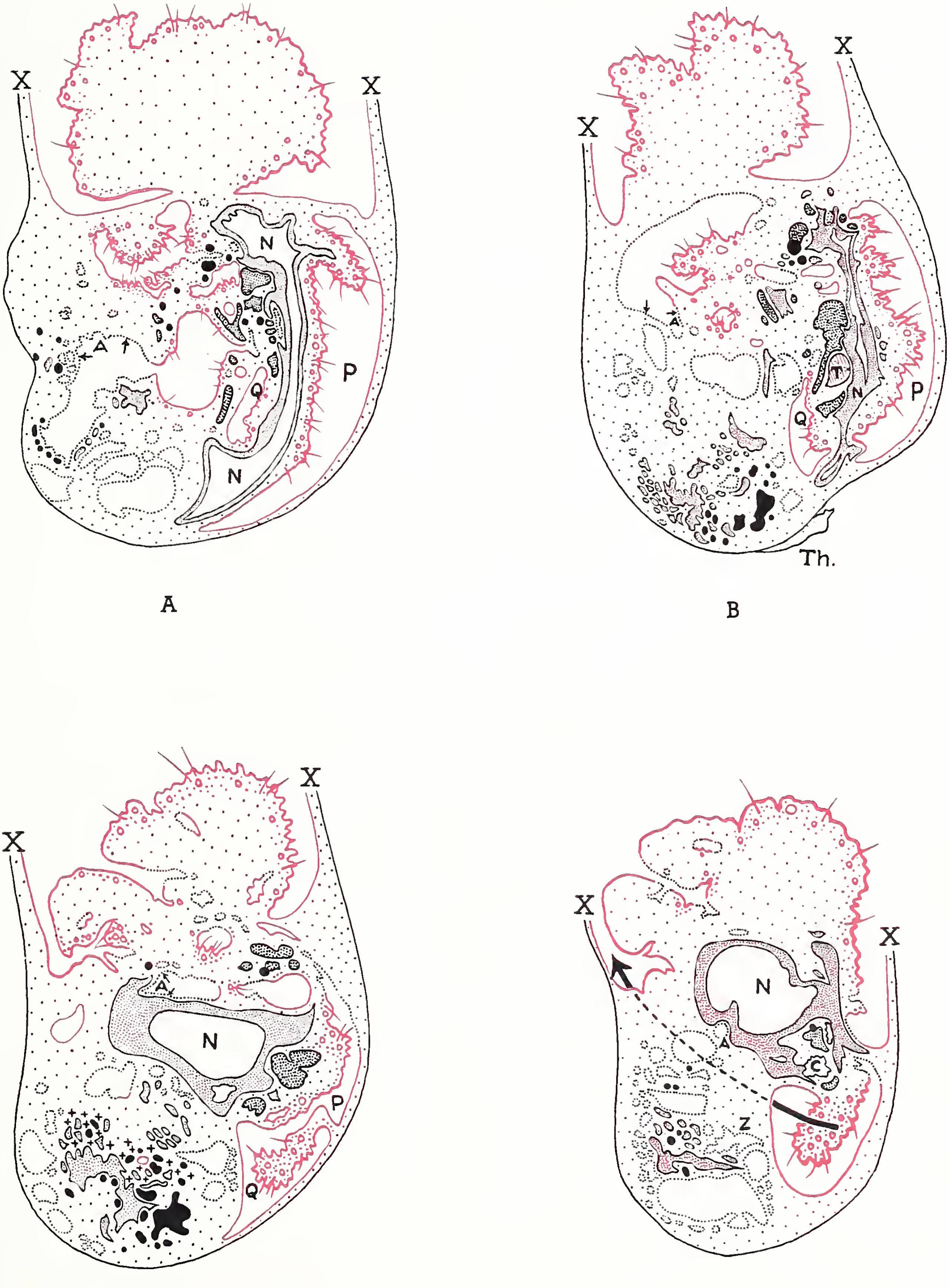
PLATE II

DIAGRAM OF FOUR SLABS OF A MEDIASTINAL TERATOMA

(Also Plate I, Fascicle 9, First Series, Teratomas. Atlas of Tumor Pathology)

Epidermis, hairs, and skin glands	
Central nervous tissues	
Main mass of nervous tissues with ependyma-lined cavity	N
Choroid plexus	C
Cartilage	
Bone	
Respiratory glandular cavities	
Alimentary glandular cavities	
Renal tissue	
Tooth (see also figs. 42 and 43)	T
Main cyst wall	X
Skin cavities, P and Q (A, B, C), continuous with main cavity as indicated by arrow (D)	
Tag of adherent thymus	Th
Cavity partly lined by endometrium-like tissue	Z

PLATE II



A

B

C

D

considerations were dealt with in the introductory section of this volume (see Classification of Gonadal and Extragonadal Teratomas). At this time, our purpose is only to stress that all histologic variants of tumors occurring in the gonads and considered to be of germ cell origin, also occur as primary tumors in the mediastinum (Bergh et al.; Cox; Martini et al.; Recondo and Libshitz). "Pure" germ cell tumors constitute only about 1 percent of all mediastinal tumors (Saegesser et al.). Their microscopic appearance is identical to their gonadal counterparts (figs. 42–45).

A series of 30 germ cell tumors of mediastinal origin reported by Martini and co-workers, from the Sloan-Kettering Cancer Center, showed 14 tumors of "pure" histologic pattern and 16 of "mixed" type. The former comprised 10 cases of pure seminoma and 4 of embryonal carcinoma; the latter group was made up of combinations of embryonal carcinoma with seminoma (2 cases), with teratoma (10 cases), and with choriocarcinoma (4 cases). Recondo and Libshitz, from the M. D. Anderson Hospital, described 17 cases of malignant germ cell tumors of the mediastinum. Eleven were of "pure" histologic type, 5 of which were seminomas. The 6 tumors of mixed composition comprised different germ cell tumor patterns in combination with teratomatous elements. The high prevalence of "pure" seminoma in these series contrasts with the low figures reported from other sources (Bergh et al.; Saegesser et al.). It is of considerable importance to try to ascertain the true incidence of the different patterns, because of their different prognostic implications (see Prognosis). In Table 3 are listed the different histologic types of mediastinal germ cell tumors found in five reported series, with the number of cases represented in each category. Frequent use of the term "teratocarcinoma" in the communications is regrettable. This term is left undefined, or is defined as tumors containing mature and immature tissues, but without any indication as to what kind of tissue was considered to be the malignant component. Although we disapprove of the use of such a word, we have transferred it from the literature in compiling the pertinent table, assuming it indicates the capacity of the germ cell tumor tissues to differentiate along nongerminal lines. Adding up all malignant germ cell tumors of these five series yields a total of 83 cases, out of which 24, or about one-third (28.9 percent), were "pure" seminomas. In each of these series, a "pure" pattern of choriocarcinoma was very infrequently seen, and no specific mention was made of a yolk sac tumor pattern. The latter tumor only rarely originates within the mediastinum. Mukai and Adams reviewed the subject in 1979. Up to that time, only 12 cases had been reported in this anatomic site. Both choriocarcinoma and yolk sac tumor of the mediastinum are more common in males than females, and preferentially affect young adult patients (Lynch and Blewett; Mukai and Adams).

Differential Diagnosis. Help in the clinical differential diagnosis of mediastinal tumors is traditionally derived from two considerations: the selectivity of occurrence of certain tumors in specific mediastinal compartments, and the different incidence of certain lesions as a function of the patient's age. Teratomas most often arise in the anterior mediastinal compartment, in close apposition to the base of the heart. In children, other anterior mediastinal mass lesions are: thymic cyst or hyperplasia, germinoma, vascular tumor, and lymphoma. *Posterior* mediastinal tumors in children are

Table 3

TERATOMAS AND GERM-CELL TUMORS OF THE MEDIASTINUM

	Recondo and Libshitz	Bergh et al.	Saegesser et al.	Cox	Martini et al.	TOTAL
"Pure" Histologic Type						
Seminoma	5	2	1	6	10	24
Embryonal Carcinoma	1	1	—	5	4	11
Choriocarcinoma	1	—	1	2	—	4
"Teratocarcinoma"	4	4	2	7	—	17
"Mixed" Histologic Type						
Embryonal Carcinoma & "Teratocarcinoma"	2	—	—	—	10	12
Embryonal Carcinoma & "Teratocarcinoma" & Seminoma	1	—	—	—	—	1
Embryonal Carcinoma & Seminoma	2	—	—	3	2	7
Embryonal Carcinoma & Choriocarcinoma	—	—	—	—	4	4
"Teratocarcinoma" & Seminoma	1	—	1	1	—	3

predominantly neurogenic tumors, enterogenous cysts, and developmental lesions. *Middle* mediastinal masses include lymphoma and inflammatory disease of lymph nodes, cysts, and duplications. About 80 percent of all mediastinal masses in children are either neurogenic tumors, teratomas, or enterogenous cysts. Of 105 mediastinal cysts and tumors seen at the Mayo Clinic between 1935 and 1968 in pediatric patients, 37 were neurogenic tumors, 21 were teratomas, 9 were lymphomas, 7 enteric cysts and duplications, and the remainder were distributed among a number of miscellaneous conditions (Whittaker and Lynn). Vascular tumors and cystic hygromas also occur, particularly in the upper reaches of the mediastinum ("superior mediastinum"). Accordingly, most of the malignant mediastinal tumors in children are either neurogenic, teratomatous, or vascular (Tandon; Wychulis et al.).

Whereas the different types of lesions follow the same anatomic distribution in adults, certain lesions are very uncommon in the pediatric patient, and therefore pose a problem of differential diagnosis almost exclusively in adults. These include pericardial coelomic cysts, retrosternal goiter, and intrathoracic parathyroid tumors. Likewise, thymoma is exceptional in children and tends to be more common with increasing age (Rosai and Levine). In contrast, thymic hyperplasia may be confused

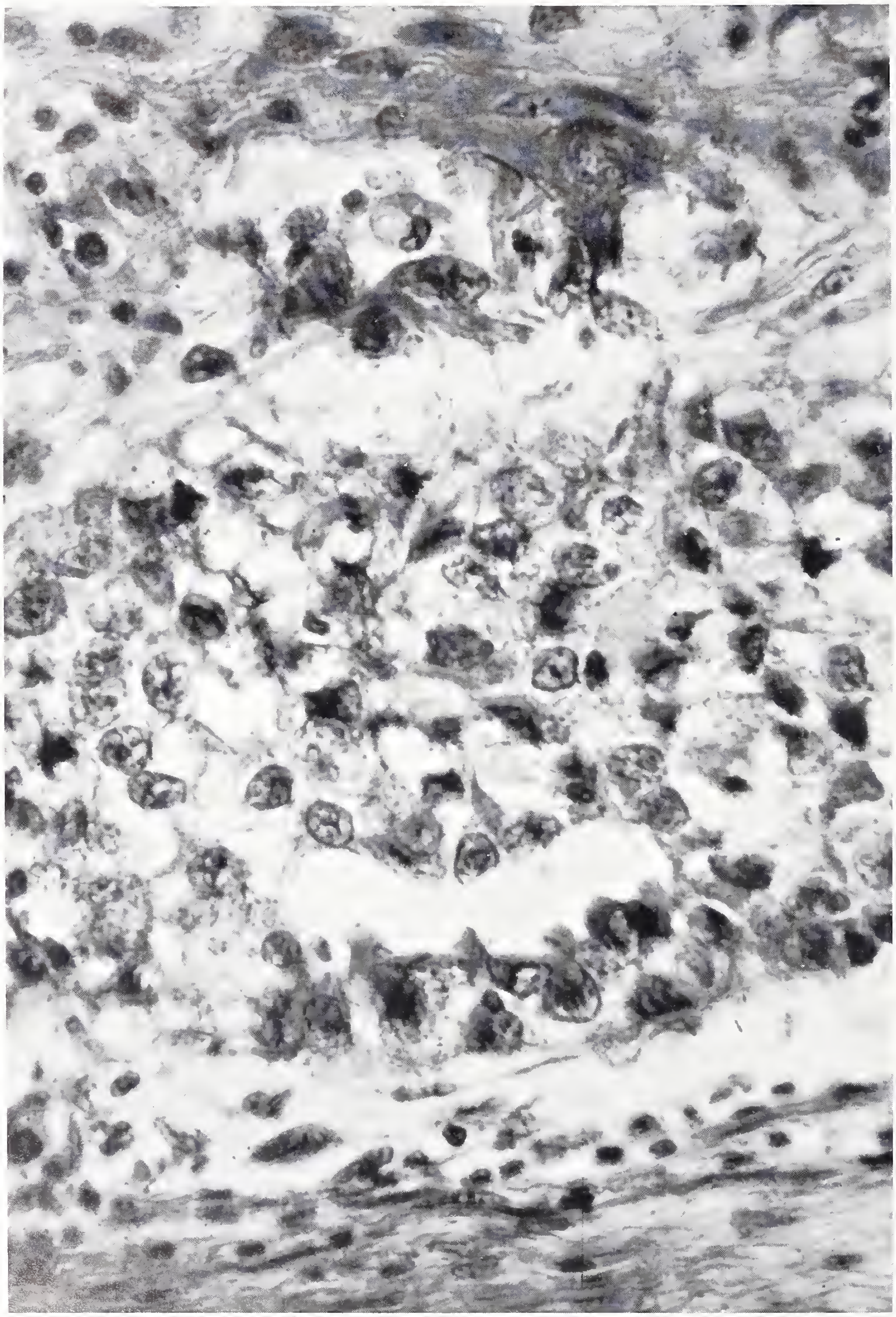


Figure 42
MEDIASTINAL TERATOMA
Area of embryonal carcinoma, indistinguishable from the gonadal tumor of the same name, in a primary malignant mediastinal teratoma. X500.

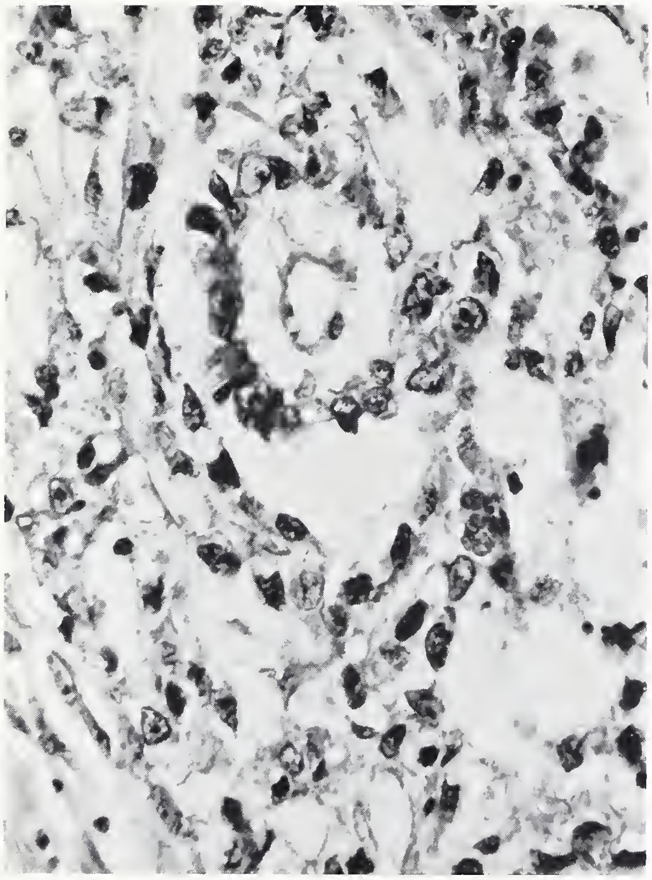


Figure 43
MEDIASTINAL TERATOMA
"Glomeruloid," or "Schiller-Duval" structure in a mediastinal tumor with the histologic appearance of endodermal sinus tumor. A central vessel is surrounded by a peripheral epithelial mantle. X275.

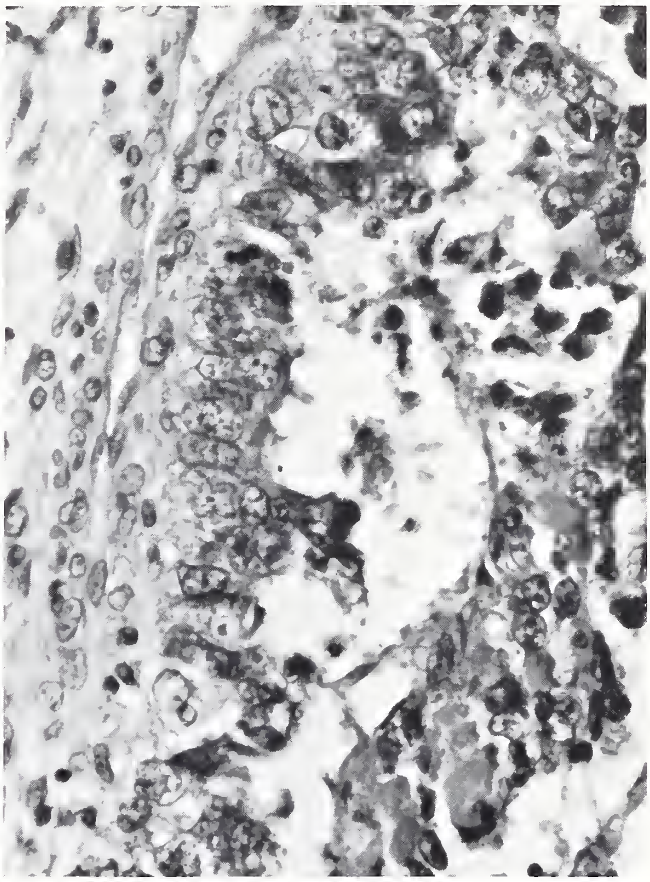


Figure 44
MEDIASTINAL TERATOMA
"Germ cell tumor" area in a malignant mediastinal teratoma. Epithelial cells contain a hyalin, PAS-positive substance largely filling the cytoplasm. Alpha-1-fetoprotein was present in the serum. X450.

with an anterior mediastinal tumor in children. Although the normal weight of the thymus is highly variable, often casting suspicion on the validity of the use of the term "hyperplasia," there is little question that this condition exists: a histologically normal thymus weighing 224 g. has been reported (Katz et al.), i.e., about 10 times the normal mean weight at birth (Boyd). Distinction between neoplastic and nonneoplastic masses may be impossible in such cases, prior to operation. It is currently held that a large thymic shadow on x-ray films bears no relationship to respiratory symptoms, when these are present (Caffey).

Bronchogenic cysts account for less than 5 percent of mediastinal masses in children, but should be distinguished from teratomas, clinically and pathologically. These lesions occur in the vicinity of the carina or major bronchi, to which they may be adherent. This relationship accounts for signs and symptoms of lower airway obstruction, atelectasis, or air-trapping emphysema, even when the cysts are so small that they are totally inapparent on the standard x-ray films (Eraklis et al.). Histologically, their walls are composed of tissues normally encountered as bronchial constituents; cartilage, mucous glands, and ciliated columnar epithelium. Of even low-

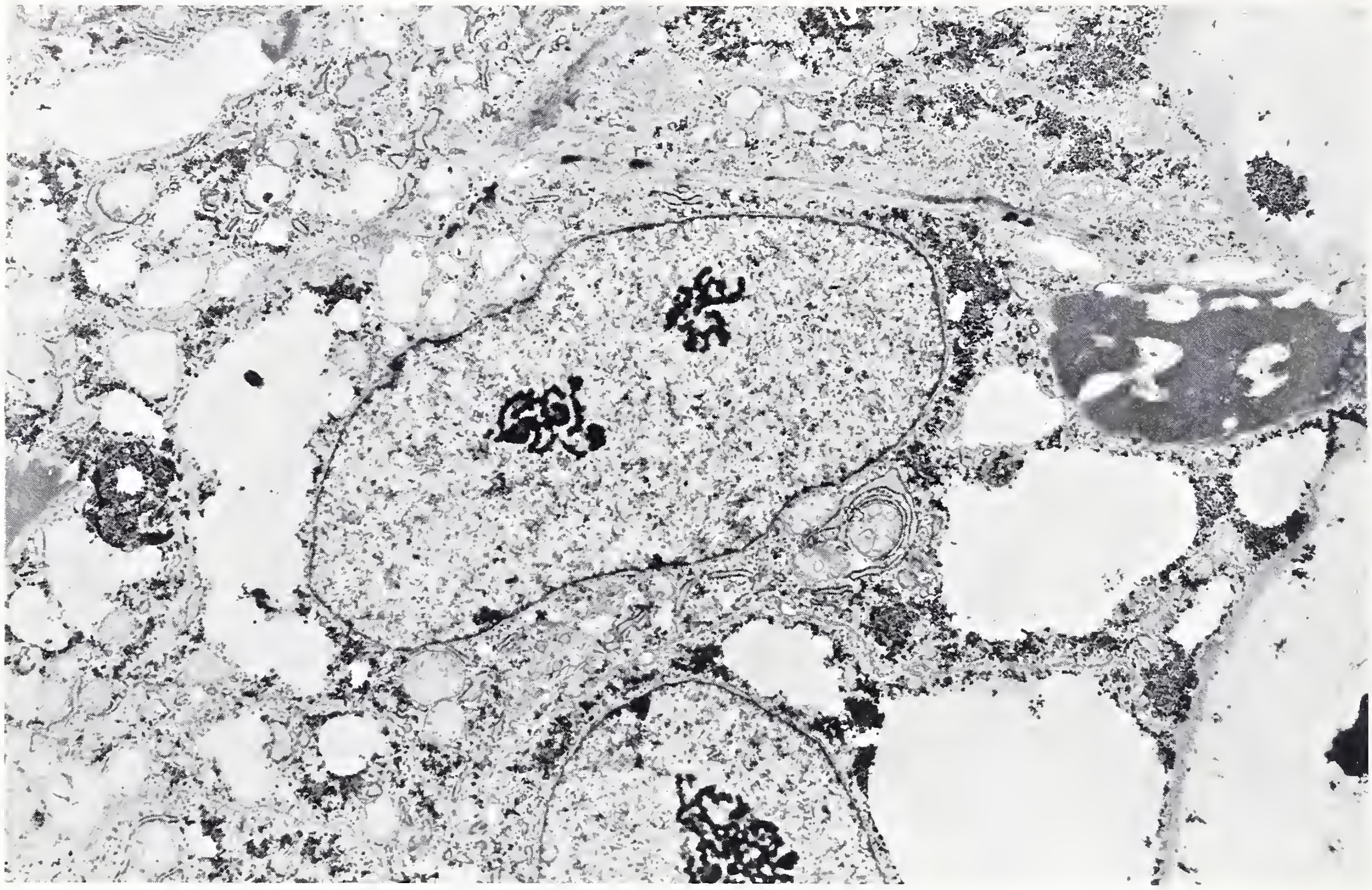


Figure 45
MEDIASTINAL TERATOMA
Ultrastructural appearance of malignant mediastinal "germ cell tumor" area of a teratoma. The peculiar nucleoli, with complex development of nucleolonemata, are characteristic of germ cell tumors. Extracellular electron-dense deposits correspond to PAS-positive material identified by light microscopy, which is synthesized by the cells and extruded to the extracellular space. X16,500.

er frequency are thymic cysts, i.e., cysts containing histologically identifiable thymic tissue in the wall, and usually a flattened cellular layer lining the cavity. Rarely, thymic cysts may present at the base of the neck (see Teratomas of the Neck). Among the uncommon lesions are cysts lined by alimentary tract mucosa. So-called "enteric cysts" of the mediastinum are usually seen in the posterior mediastinal compartment, often close to the esophagus, to which they may be joined through anatomic connections of variable importance. Those lined by gastric mucosa are almost always in the right mediastinum (Williams and Johnson). Bronchogenic and gastroenteric cysts both arise by faulty embryogenesis of the foregut and its primitive tracheobronchial bud (Shillitoe and Wilson). Posterior mediastinal cysts of developmental origin, such as "enteric cysts," often associate with malformations of the spinal column and cord; a roentgenologic examination for a posterior mediastinal mass is incomplete if it has not properly exposed the vertebrae.

Until recently, the differential diagnosis between teratoma and developmental cysts appeared simple and straightforward. Several reports have appeared in recent years, however, that postulate the maturation of metastases of malignant testicular teratoma, in such a way that the metastatic foci eventually become indistinguishable from a primary benign teratoma, or an enteric or bronchogenic cyst (Dees; Merrin et al.; Smithers; Snyder). In most cases, the primary tumor has been a testicular malignant teratoma and the metastases have evolved to well differentiated tissues of the three germ layers; less commonly, derivatives of a single germ layer are apparent and the metastasis may be indistinguishable from a primary hamartoma or a mediastinal enteric cyst (Stechmiller et al.). These facts insistently remind us of the need to rule out an occult testicular neoplasm in all cases of mediastinal teratoma occurring in males. The proposition that all extragonadal "germ cell neoplasms" might represent metastases from an occult testicular primary (Meares and Briggs) seems untenable for the following reasons: the anterior mediastinum is not a common metastatic site for testicular malignancies; females are sometimes affected; a testicular primary has not become apparent in cases with long survival; and scarred lesions suggestive of the former existence of a testicular primary tumor (Azzopardi et al.) are not invariably present at autopsy (Cox), even when the gonads are extensively investigated at postmortem (Recondo and Libshitz; Saegesser et al.). On the other hand, it is easy to agree that a gonadal primary tumor should be ruled out in all cases of extragonadal teratoma, but it is not easy to agree on the appropriate means to eliminate such a possibility. A more detailed discussion of this problem is presented in the chapter on Retroperitoneal Teratomas.

Prognosis. The prognosis of patients with benign teratomas of the mediastinum who have been treated by complete extirpation should be excellent. In the absence of complications, surgery achieves a complete cure in the patient with a mature, benign teratoma of low histologic grade. The malignant nature of a teratoma, however, may escape detection after incomplete sampling (Canty and Siemens). For this reason, thorough sampling is indispensable before a particular case is diagnosed as benign.

In contrast, an extremely poor prognosis appears to be associated with a mediastinal malignant tumor histopathologically characterized by a germ cell tumor component. Of the 85 cases reviewed by Cox under the designation of "teratocarcinoma," none survived. Schlumberger noted a mean survival of 5.5 months, and this dismal experience has been repeated in other series in spite of therapeutic advances (Bergh et al.; Friedman; Oberman and Libcke; Pachter and Lattes; Saegesser et al.). The suggestion has been made that therapy should be more aggressive if any hope of control of the disease is to be entertained (Cox). On the other hand, it is becoming increasingly apparent that the prognosis is not uniformly poor for all teratomas containing germ cell tumor areas, and that when the "germ cell component" is seminomatous (germinoma), the prognosis is considerably better. The influence of the different histologic types on prognosis is obscured by the practice of encompassing structurally heterogeneous tumors under the common name of "malignant teratoma," "teratocarcinoma," or other all-inclusive terms. Nonetheless, in those reports in which detailed information is given, long-term survivors usually had seminoma-like tissue as the malignant component (Bergh et al.). The seminomatous areas are malignant and capable of distant spread, especially to lymph nodes and bone; the former occur early and the latter usually late in the course of the disease. Two of 5 mediastinal seminomas in the series reported by Recondo and

Libshitz and 6 of 10 in that of Martini and associates gave rise to osseous metastases. Metastases to bone are rare with other germ cell tumors of mediastinal origin, perhaps due to their rapidly fatal course.

The good local control that has been achieved for mediastinal seminomatous tumors by combined surgery and radiotherapy has not been matched in other germ cell tumors, regardless of the therapeutic approach. Mediastinal germ cell tumors have a worse outlook than their testicular counterparts, probably on account of their comparatively late clinical detection (Recondo and Libshitz). Of the 12 cases of "pure" yolk sac tumor of the mediastinum reviewed by Mukai and Adams, 7 patients had died of their tumors within one year after diagnosis. These authors concluded that only when the tumors are small, asymptomatic, and have no metastasis, can there be a chance of cure. The presence or absence of other germ cell tumor components did not seem to alter the prognosis. It seems warranted to conclude that, as in other locations, the presence of a yolk sac tumor component in a mediastinal teratoma indicates a particularly bad prognosis. Similar considerations may be made for tumors with a choriocarcinoma component (Lynch and Blewett; Peison). Information is more limited with respect to other morphologic variants and combinations thereof. All fare much worse than the radiosensitive germinoma, but there is hope that currently evolving chemotherapeutic advances might soon modify this generally grim outlook.

Treatment. Wychulis and associates reported a progressive reduction in the sizes of the mediastinal neoplasms resected over a 40-year period, implying a more aggressive attitude taken by surgeons and physicians toward the diagnosis and treatment of these lesions. Posterior mediastinal tumors, most commonly neurogenic, but sometimes teratomatous in nature (Paquet et al.), can be removed extrapleurally through a relatively small incision. "Dumbbell" tumors in the posterior mediastinum may be encountered in which there has been foraminal erosion and possibly intraspinal extension. These lesions constitute a problem that warrants neurosurgical consultation. As most mediastinal tumors project into one of the hemithoraces, surgeons often elect a lateralized incision; midline sternotomy provides adequate access to anterior mediastinal masses, including the large ones that project into both thoracic spaces.

The surgical conduct is often determined by the fact that most mediastinal tumors are benign, and can be effectively dealt with by surgical means. Since operation is both diagnostic and therapeutic, indirect procedures such as mediastinoscopy and needle biopsy are of very restricted application. A tempering consideration, however, is that mediastinal tumors constitute a heterogeneous group, often incorrectly diagnosed prior to exploration. Accordingly, whereas resection is the treatment of choice for the majority of these lesions, the surgeon should be knowledgeable of the various possibilities, and technically adept to handle the uncommon or unexpected. Radiation therapy and chemotherapy must be considered when areas of germ cell tumor are identified in a mediastinal teratoma. The radiosensitive nature of germinomas is generally well known. Advances in chemotherapy hold a real promise for improvement of the currently very poor prognosis of nonseminomatous germ cell tumors. The complexities of this rapidly advancing field determine that the choice of drugs and treatment modalities should be the domain of the specialist.

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* * *

INTRAPERICARDIAL TERATOMAS

Joël is often credited with the first description of an intrapericardial teratoma, although the lesion he described would probably be classified today as a bronchogenic cyst. By 1967 only about 30 cases of true pericardial teratomas had been described (Lubin et al.), thus reflecting the rarity of teratomas in this anatomic site. Torres-Aybar and associates found reports of 48 cases in patients of all ages, between 1890 and 1975; 24 of these tumors were seen in individuals three months of age or younger. Intraperitoneal teratomas have been said to be uncommon in Negro children, but at least five cases affecting individuals of this race have been reported from Africa (Lintermans et al.), and one of the largest tumors successfully treated occurred in a Negro female infant in the United States (Wilson et al.)

Clinical Features. As expected from their location, intrapericardial teratomas commonly result in symptoms and signs of compression of the heart and lungs by the expanding mass. These effects may be magnified by an associated pleural and pericardial effusion. When cardiopulmonary compression takes place, the possibility of pulmonary infection is enhanced, increasing the severity of the respiratory distress. Recognition of the clinical triad of cardiomegaly, muffled heart sounds, and cardiac tamponade due to clear serous fluid, may lead to early diagnosis. When these manifestations occur in an infant under the age of three months, the diagnostic suspicion of intrapericardial teratoma should be enhanced (Torres-Aybar et al.). Teratomas of the pericardium have been occasionally discovered on radiologic examination of an asymptomatic patient. This occurrence is rare in adults and truly exceptional in infants.

Gastrointestinal manifestations secondary to esophageal compression have been prominent in some cases. Willis described a 10 week old infant with dysphagia and weight loss resulting from an intrapericardial teratoma.

Roentgenologic and Laboratory Examination. Plain roentgenograms of the chest usually disclose a homogeneous mass obscuring the heart borders. The largest tumors severely distort all the normal intrathoracic structures. Lateral projections better reveal the position of the tumor. The presence of radiopaque areas characteristic of teeth has been detected (Haller et al.). Pericardiocentesis and injection of air in the pericardial sac may be required to optimally outline the contour of the tumor and to establish its independence from the heart. Angiocardiography may be required to ascertain whether the mass communicates with the intracardiac or intravascular compartments, as teratomas may rarely involve the heart (Solomon; Van der Hauwaert). This information is crucial in planning treatment, since cardiopulmonary bypass facilities must be available in the event that the tumor involves vital cardiovascular structures (Lubin et al.). With the aid of angiocardiography and pneumopericardiogram, the intrapericardial position of the mass can be established. Often this allows confirmation of displacement and compression of right-sided cardiac chambers and clockwise rotation of the heart along its longitudinal axis within the pericardial sac. Ultrasonography may, as for teratomas of other sites, contribute to establish the multicystic nature of the tumor.

Cytologic examination of the pericardial fluid has been uniformly negative for tumor cells. Pericardial fluid should be sent for cytologic and microbiologic examination each time a pericardial effusion is tapped. The presence of cholesterol (Lintermans et al.) in the fluid is nonspecific. It may reflect secretions or degenerative cell products from the teratoma.

Gross Appearance. These tumors appear as bosselated, firm to fluctuant masses that characteristically are multicystic (fig. 46). The cysts vary in size from a few millimeters to several centimeters in diameter; their contents may be serous, mucinous, or hemorrhagic. In the stroma separating the cysts are small yellow flecks of calcium or tiny islands of cartilage (Claireaux; Dabbs et al.; Deenadayalu et al.; Kulkarni). Tietze first noted the tendency of these tumors to be situated in close appostion to the right-sided heart chambers, but some tumors

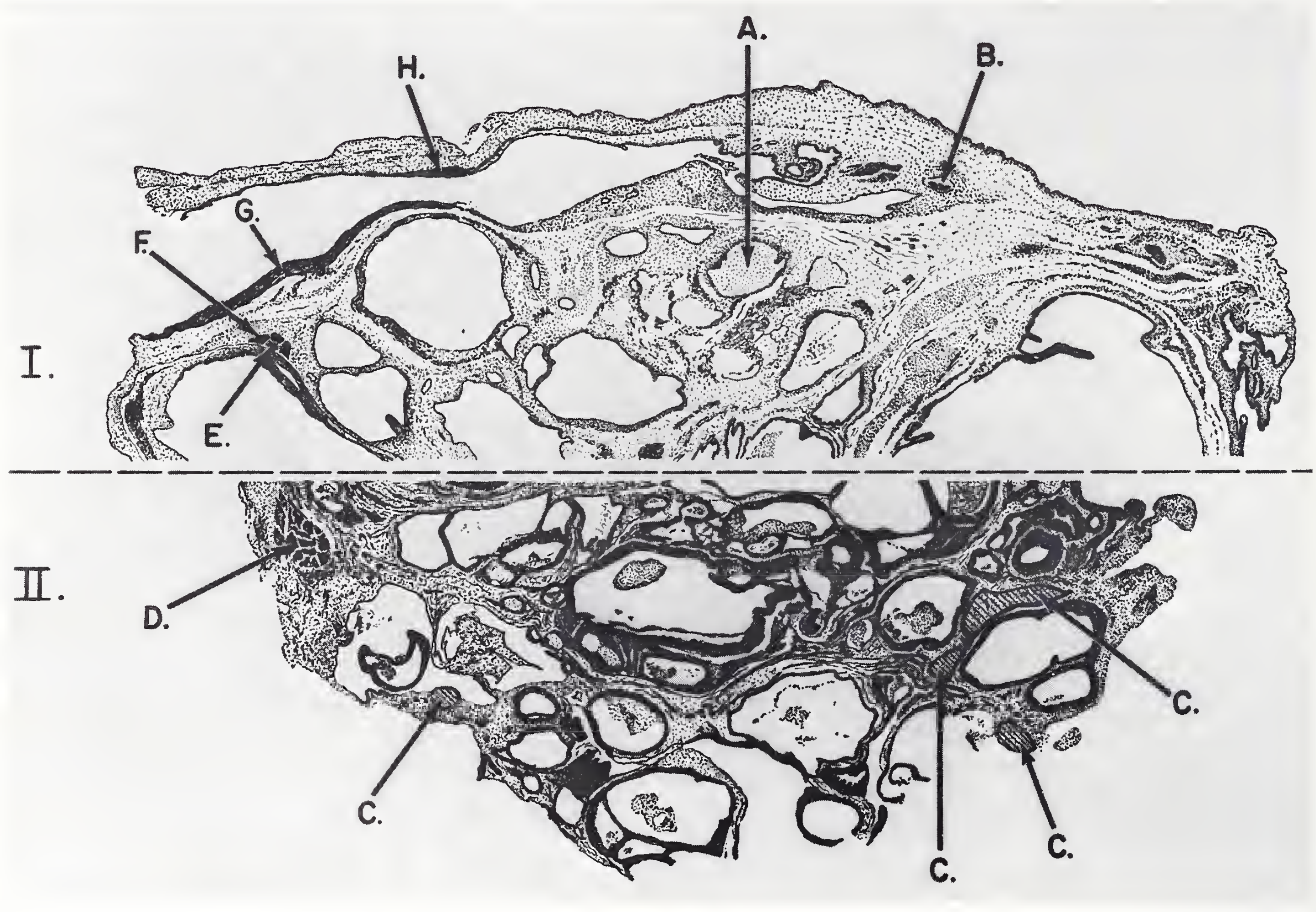

Figure 46
(Figures 46, 48-51 from same case)
INTRAPERICARDIAL TERATOMA

Drawing of macrosection of hemisected intrapericardial teratoma. Tissues present in this neoplasm included: (A) islands of neuroglia; (B) optic disc; (C) cartilage; (D) skeletal muscle; (E) liver tissue; (F) salivary gland; (G) mucus-secreting epithelium with ciliated cells; and (H) ciliated epithelium. (Courtesy of Dr. Victor Arean, St. Petersburg, FL. From Wilson, J.R., Wheat, M.W., Jr., and Arean, V.M. Pericardial teratoma. J. Thorac. Cardiovasc. Surg. 45:670-678, 1963.)

may be left-sided (fig. 47) and others may completely surround the heart.

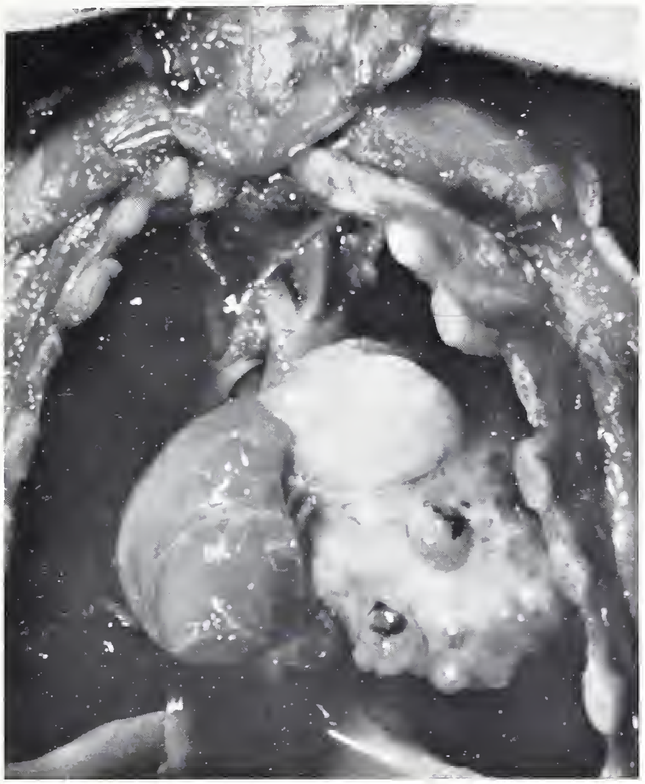

Figure 47
INTRAPERICARDIAL TERATOMA
Congenital intrapericardial teratoma arising near the root of great vessels, and encroaching upon the left hemithorax. Bosselated surface indicates its multicystic structure. (Courtesy of Dr. C. Sotelo-Avila, Houston, TX.)

Microscopic Appearance. Microscopically, the cystic spaces are usually lined with either mucus-producing columnar epithelium or ciliated epithelium. Other spaces may be lined by stratified squamous epithelium. The polycystic nature of the tumor may be so predominant as to obscure the presence of the diverse tissues expected in a teratoma. Some cases have been called "teratoid" tumors, or deemed to be malformations akin to bronchogenic cysts. However, when extensive sampling is carried out, derivatives of the three germ layers can be identified in many of these cases (figs. 48–51). Malignant tissues have not been identified as components of intrapericardial teratomas.

Differential Diagnosis. The differential diagnosis of a large cardiac silhouette in infancy includes myocarditis, endocardial fibroelastosis, storage disease, or idiopathic myocardiopathy. Once it is learned that the mass is independent of the heart, bronchogenic cysts must be included in the differential diagnosis (Deenadayalu et al.; Yeoh et al.). In general, teratomas are discovered in infants and children younger than one year of age, while bronchogenic cysts manifest past this age, and may be asymptomatic

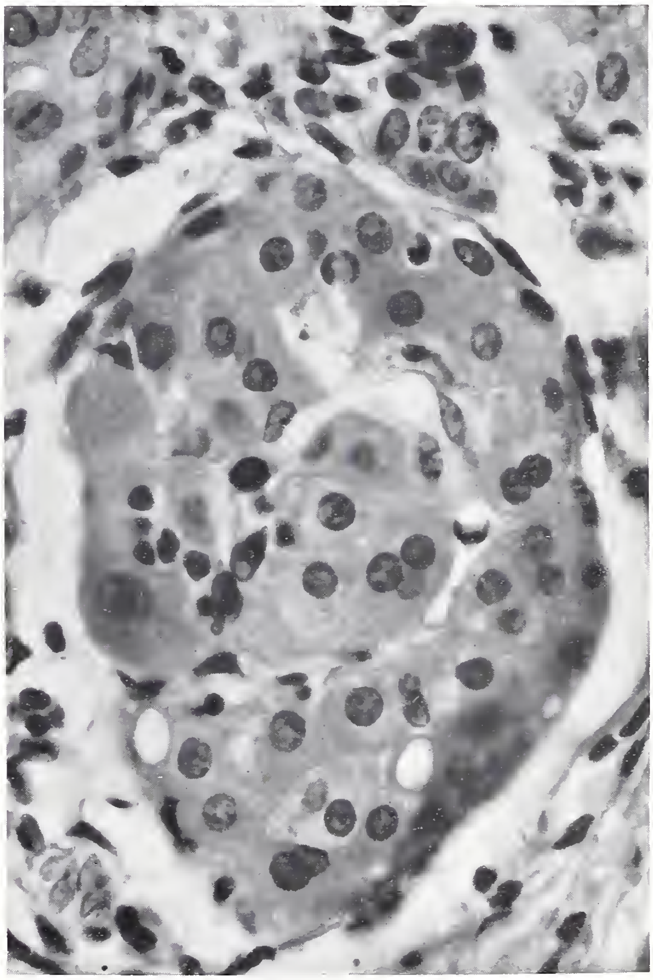

Figure 48
INTRAPERICARDIAL TERATOMA
Clusters of cells morphologically identified as hepatocytes (same case as fig. 46). X480. (Courtesy of Dr. Victor Arean, St. Petersburg, FL.)

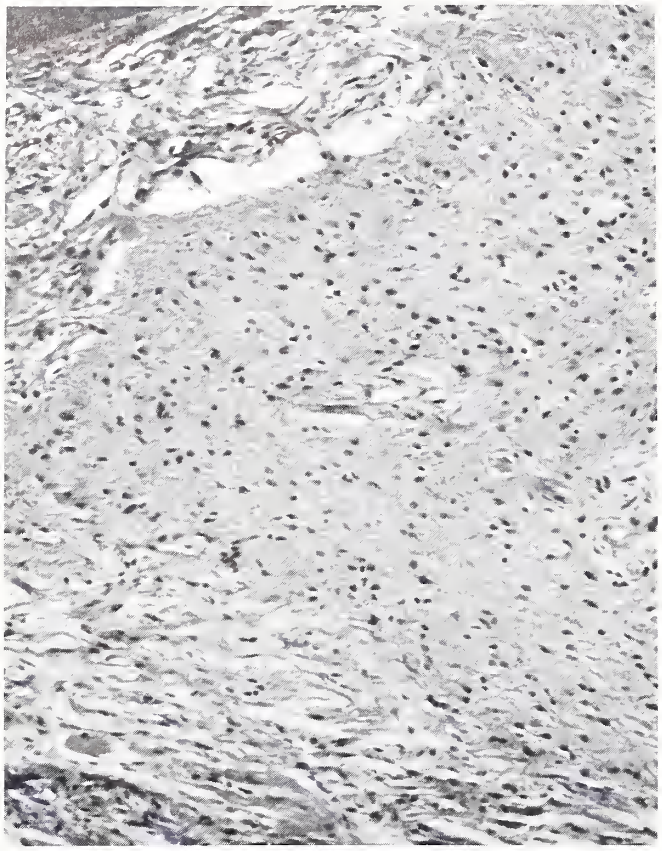

Figure 49
INTRAPERICARDIAL TERATOMA
Mature glia in "brain-like" area of case illustrated in figure 46. X120. (Courtesy of Dr. Victor Arean, St. Petersburg, FL.)

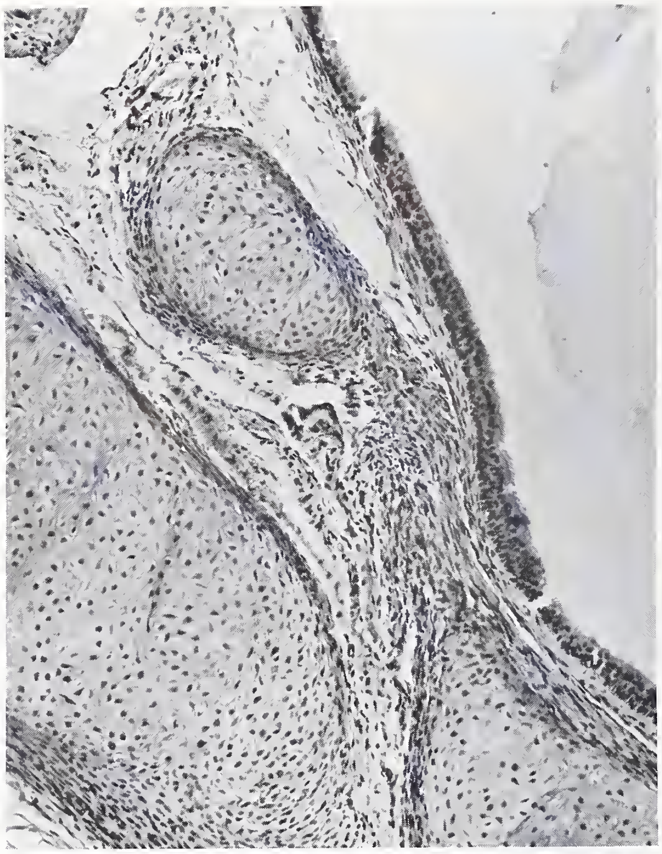

Figure 50
INTRAPERICARDIAL TERATOMA
Cartilage plates and cavity lined by cilated epithelium. X180. (Courtesy of Dr. Victor Arean, St. Petersburg, FL.)

(Yeoh et al.). Wilson and associates reviewed the cases of intrapericardial tumors reported between 1890 and 1962, and concluded that 40 percent were true teratomas, and the remainder were bronchogenic cysts or "dermoid cysts." On occasion, a "coelomic" or pericardial cyst, lined by flattened mesothelial cells, will grow into the pericardial cavity.

Prognosis. At least three deaths from exsanguination have occurred during surgical removal of an intrapericardial teratoma (Yeoh et al.). Thus, the prognosis of these tumors is largely dependent upon their anatomic localization; prompt recognition may make the difference between complete cure and death from cardiac tamponade. Symptoms and signs of neonatal respiratory distress secondary to a mediastinal tumor should be considered an emergency (Haller et al.). Such an emergency is particularly apparent in intrapericardial tumors.

Treatment. Pericardial taps may afford considerable relief of the manifestations of cardiac compression due to an associated effusion. This procedure may be, on occasion, temporarily life-saving. The primary treatment of this condition is removal of the mass, which should be performed as soon as feasible. Factors complicating surgical treatment are the presence of associated infection, which is sometimes accompanied by purulent effusion, and strong attachment of the tumor to the adventitia of the great vessels.

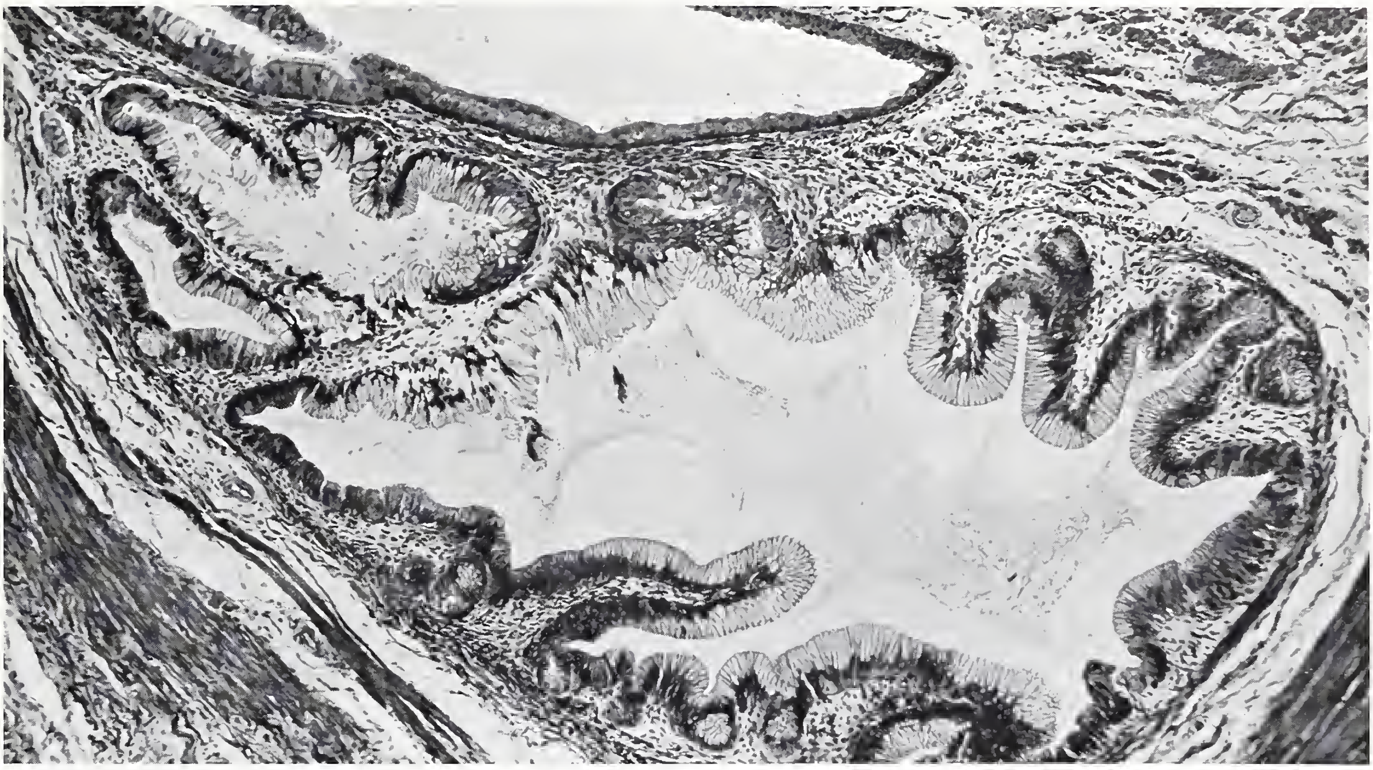

Figure 51
INTRAPERICARDIAL TERATOMA
Glands lined by mucus-producing tall epithelium in intrapericardial teratoma. X410. (Courtesy of Dr. Victor Arean, St. Petersburg, FL.)

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TERATOMAS OF THE ORBIT

SYNONYMS AND RELATED TERMS: Teratoma congenitum beningum orbitae; cystic teratoma of the orbit; neonatal orbital teratoma; giant orbital cystic teratoma; congenital teratoid cyst of the orbit; organoid polycystic teratoma of the orbit; retrobulbar teratoid tumor; dermoid cyst of the orbit; cephaloma orbitae posterior; orbitopagus parasiticus.

General Considerations. Teratomas originating within the orbit are extremely uncommon. Of a total of 1495 teratomas and "dermoid cysts" seen at the Mayo Clinic between 1910 and 1935, only 6 had an intraorbital origin (New and Erich). Similarly, of 900 intraorbital tumors filed in the Pathology Department of Cairo University, only 1 was a teratoma (Mortada). Communications in the medical literature have commonly dealt with single case reports. It is noteworthy that less than a hundred such instances are recorded, in spite of the known proclivity to publish odd and striking cases, and despite knowledge of the existence of this lesion dating back over 100 years (Bröer and Weigert; Holmes). Alkemade reviewed the literature in 1976, and found that 60 percent of the published cases had occurred in Europe, 20 percent in the United States, and 20 percent in the rest of the world. A definite preponderance of females over males (14:5) has been noted, as well as a slight preference of the tumor for the left eye over the right eye (20:13).

Clinical Features. In the majority of cases the tumor has reached a large volume by the time the child is born. The resulting appearance is dramatic; the infant's eye protrudes through a distended palpebral aperture, literally pushed out of its socket, its extrinsic muscles stretched taut over the mass and within view. Not all cases reach these massive dimensions, and the degrees of proptosis and associated edema and congestion of the periocular structures may fall short of the dramatic appearances that have often been depicted. Because the bony orbit is shaped like a pyramid oriented laterally, a retrobulbar teratoma tends to push the ocular globe along the paths of least resistance, in a temporal and downward direction. As a result, when the tumor has grown to large dimensions, the soft tissues of the face are slightly displaced on the affected side, and ipsilateral downward deviation of the corner of the mouth is often seen. Teratomas of possible congenital origin have been allowed to go untreated for nearly 40 years (Azzolini and Bistolfi), producing expansion of the surrounding bony structures and spectacular deformities. Even these large tumors have been histologically and clinically benign.

Laboratory and Roentgenologic Examination. X-ray films ordinarily show a widened, distended orbit, with normal sutures and no signs of bony erosion or intracranial hypertension. The presence of areas of calcification, and sometimes organoid formations, such as teeth (Michail), may suggest the teratomatous nature of the tumor. Ultrasound has more recently been used to reveal the cystic component of the teratoma (Hann et al.). Undoubtedly, computerized tomography shows the greatest promise as a diagnostic tool in the preoperative evaluation of intraorbital masses, and in the assessment of proptosis in general. At the present time, experience with this technic has not become generalized enough to permit any definite statement about its precise advantages and limitations in the diagnosis of specific types of intraorbital tumors. Standard roentgenograms and tomographic studies are of invaluable aid in determining the extent of the disease and in planning the surgical approach. It is hoped that greater sophistication in diagnostic technics and increased awareness of the natural history of these tumors will result in earlier intervention and improved outcome, but it must be remembered that frequently the child is born with a tumor that is already far advanced (pl. III-A; figs. 52, 53).

Gross Appearance. These tumors have varied in size from a few centimeters to about 15 cm. in greatest diameter at the time of operation. There is nothing in their gross appearance that would set them off from teratomas of other sites. Cystic and solid components are regularly encountered. In the solid areas, foci of cartilage and bone can sometimes be identified grossly. The tumors are sharply delimited or truly encapsulated (figs. 54–56).

In rare instances in which an intracranial portion was discovered, as in the example

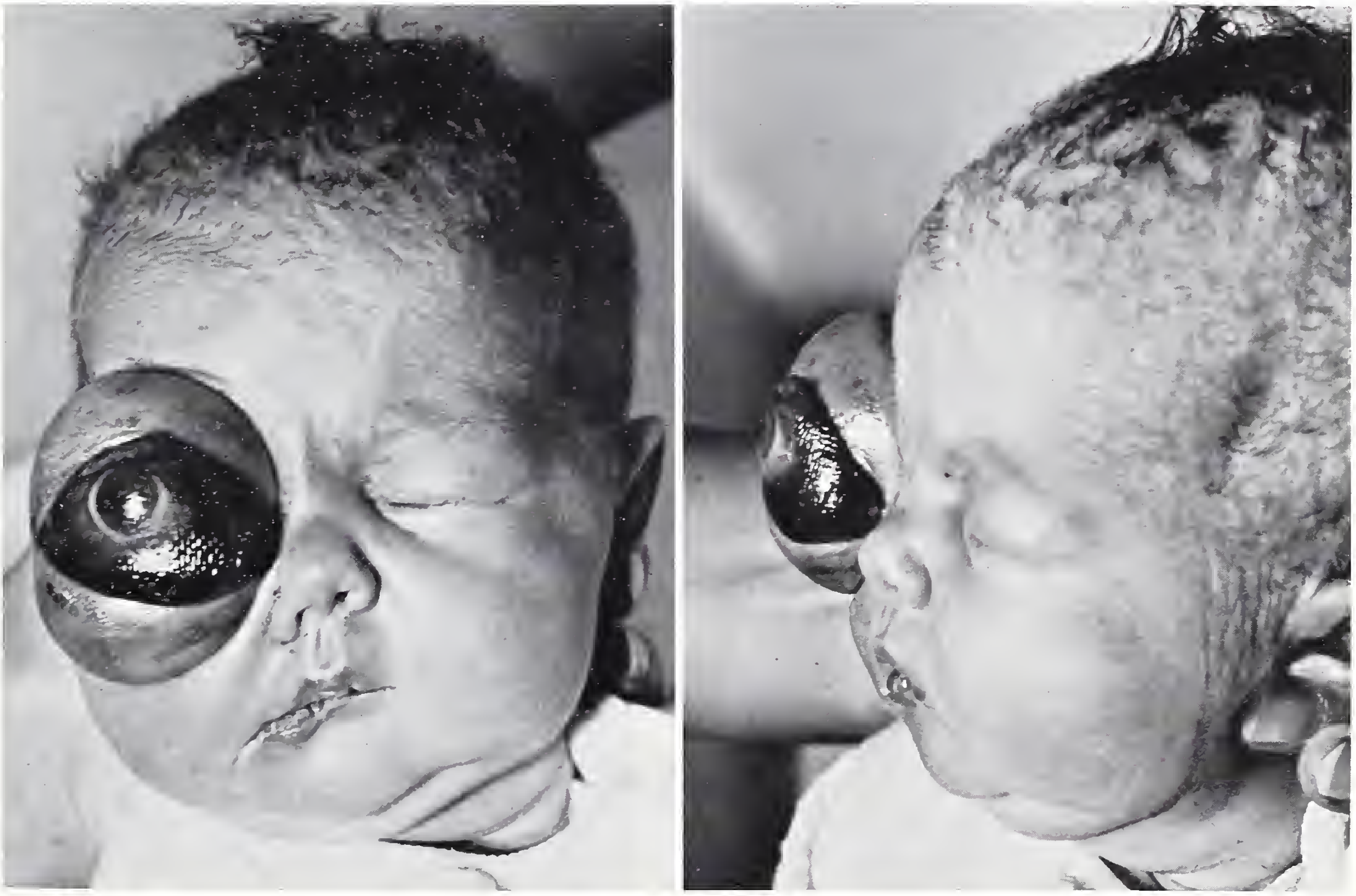

Figure 52
(Figures 52-59 from same case)
TERATOMA OF THE ORBIT
Front and lateral preoperative views of a congenital intraorbital teratoma. The eye has been pushed out of the orbit by a well encapsultated tumor growing behind it. Note dry and hemorrhagic appearance of the ocular globe, compressed by the expansile mass. (Courtesy of Dr. P. P. H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

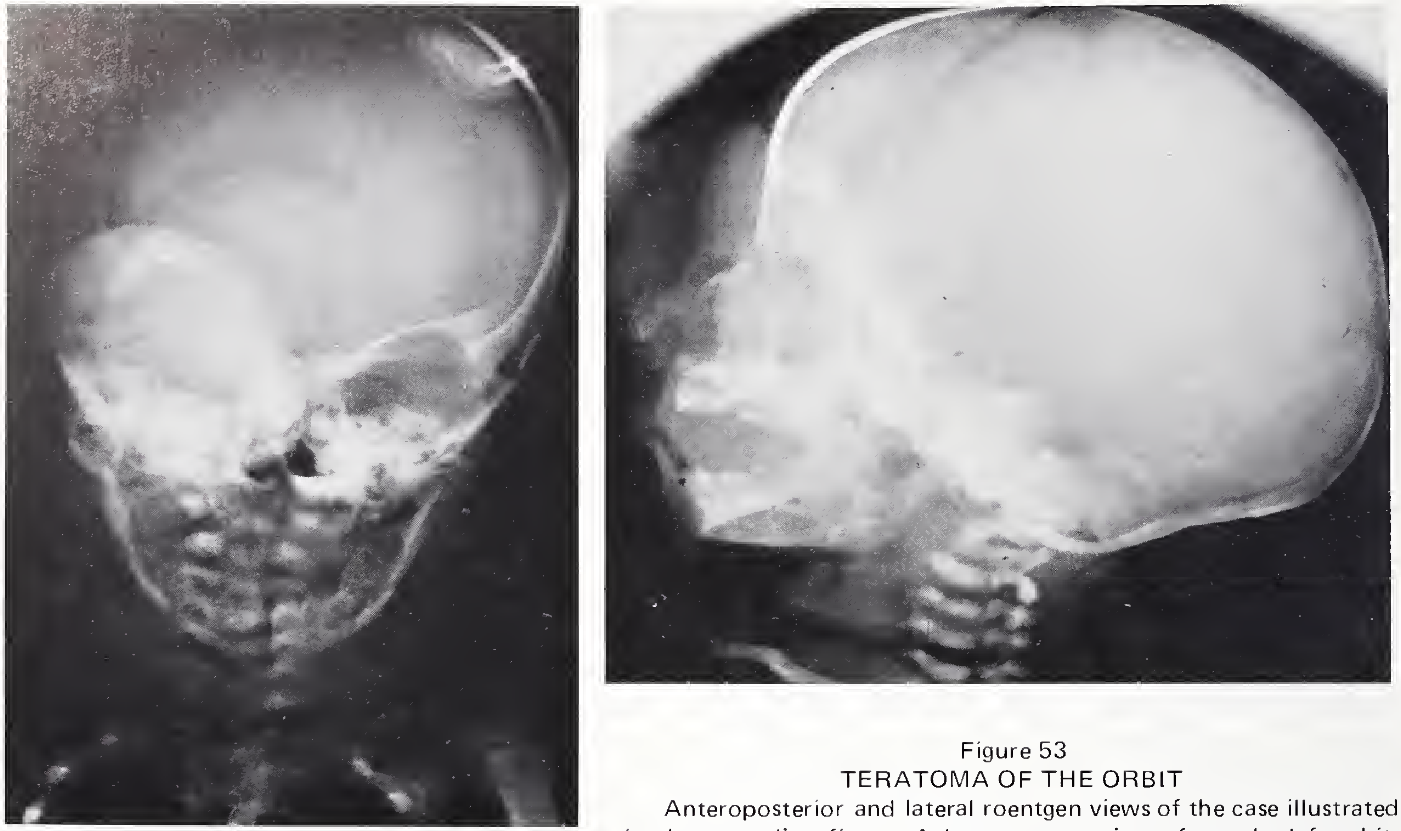

Figure 53

TERATOMA OF THE ORBIT

Anteroposterior and lateral roentgen views of the case illustrated in the preceding figure. A large mass projects from the left orbit, distending its bony walls without destroying them. (Courtesy of Dr. P. P. H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

described by Viana (intracranial nodule the size of a "pigeon's egg"), the endocranial growth remained separate from the cerebrum by the dura of the base of the skull, which was nonadherent.

Microscopic Appearance. The characteristic disorderly aggregation of well differentiated tissues of diverse origin that is the chief defining element of benign teratomas is clearly manifested by these tumors. Alkemade analyzed the available histologic reports and concluded that in 31 cases, tissues from the three germinal layers were found, whereas in 11 other cases, tissues from only two germinal layers were seen. In 10 of these 11 tumors, the tissues were derivatives of ectoderm and mesoderm, and in the remaining case, mesoderm and endoderm were represented. Thus, it appears that endodermal tissues are in-

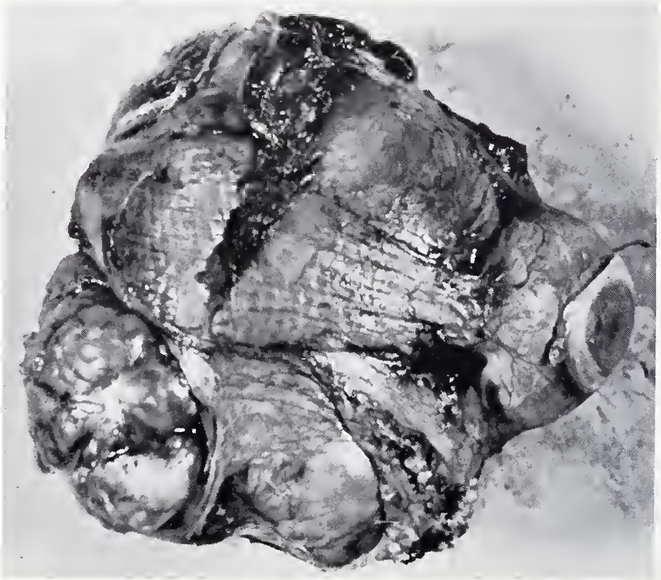

Figure 54

TERATOMA OF THE ORBIT

Gross appearance of resected specimen. The retro-ocular tumor appears as a multilobulated mass stretching the ocular muscles over its surface. (Courtesy of Dr. P.P.H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

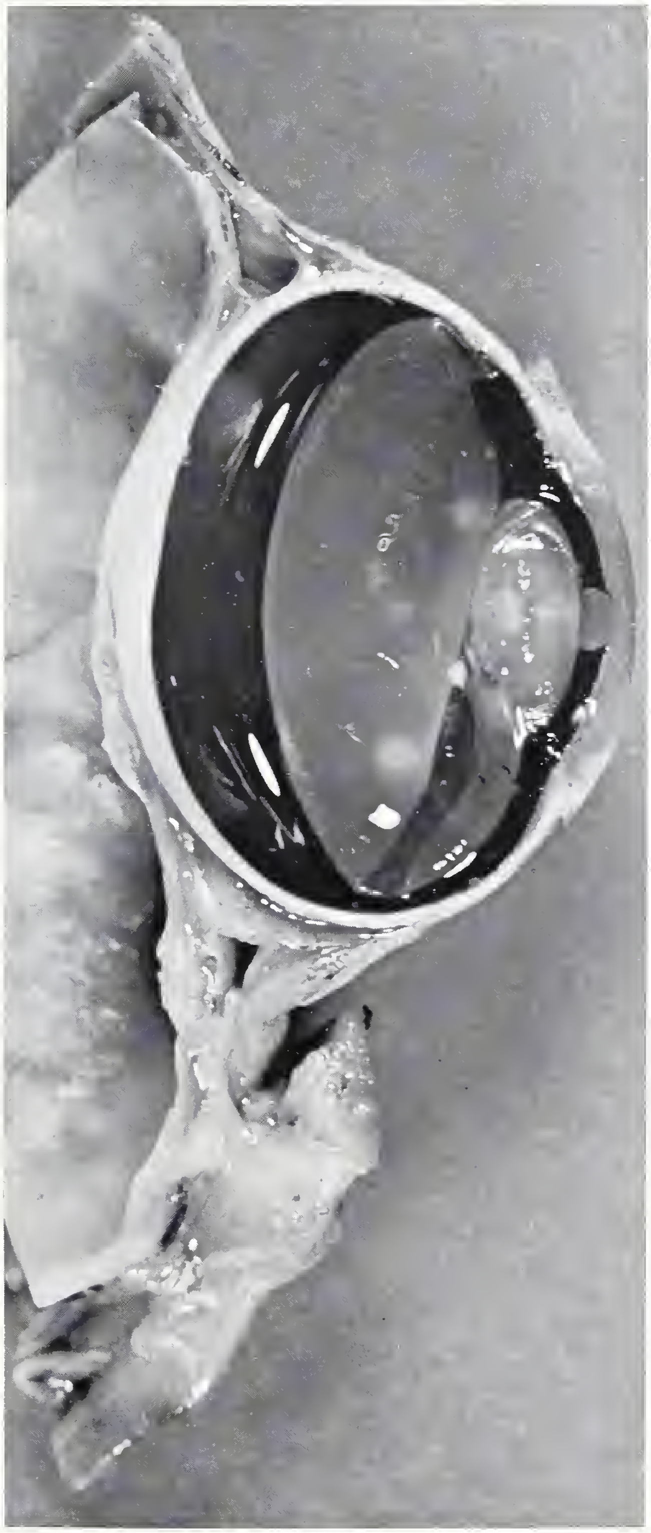

Figure 55
TERATOMA OF THE ORBIT
Cut surface of the ocular globe and the retro-ocular portion of the teratoma immediately in contact with the globe demonstrates the largely cystic nature of the tumor. (Courtesy of Dr. P. P. H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

frequent in these tumors. Skin and its adnexa, fibrous tissue, adipose tissue, muscle, cartilage, bone, and glandular epithelium are almost always seen, whereas the presence of either renal, ovarian, or testicular elements has not been documented in teratomas of the orbit (figs. 57–59). Immature neural tissue may be encountered, but germ cell tumor tissues have not been documented in this location.

Differential Diagnosis. The most important differential diagnosis, because of the implications to survival, is with malignant tumors. The most common primary orbital malignancy of childhood is rhabdomyosarcoma, even though the practicing ophthalmologist encounters this lesion only rarely. In approximately half the cases, rhabdomyosarcoma of the orbit presents as a mass growing behind the ocular globe, rapidly pushing the globe from behind; the remainder of the cases are distributed along the four orbital quadrants. Distinction from teratoma should be facilitated by the difference in the age of onset of these two tumors. Rhabdomyosarcoma of the orbit is uncommon in infancy. Knowles and associates combined the data obtained in four major published series, and noted that the average age of onset of 161 pooled cases of intraorbital rhabdomyosarcoma varied only from 7.2 to 8.2 years, regardless of the institutional setting. Although each of the series analyzed by the latter authors contained an exceptional case of orbital rhabdomyosarcoma in a newborn infant, such an occurrence is extremely rare.

Far more common conditions presenting as rapidly evolving exophthalmos in a young child are benign vascular lesions, i.e., hemangiomas and lymphangiomas. Cutaneous hemangiomas may coexist with the intraorbital vascular tumor, thereby providing circumstantial evidence useful to the

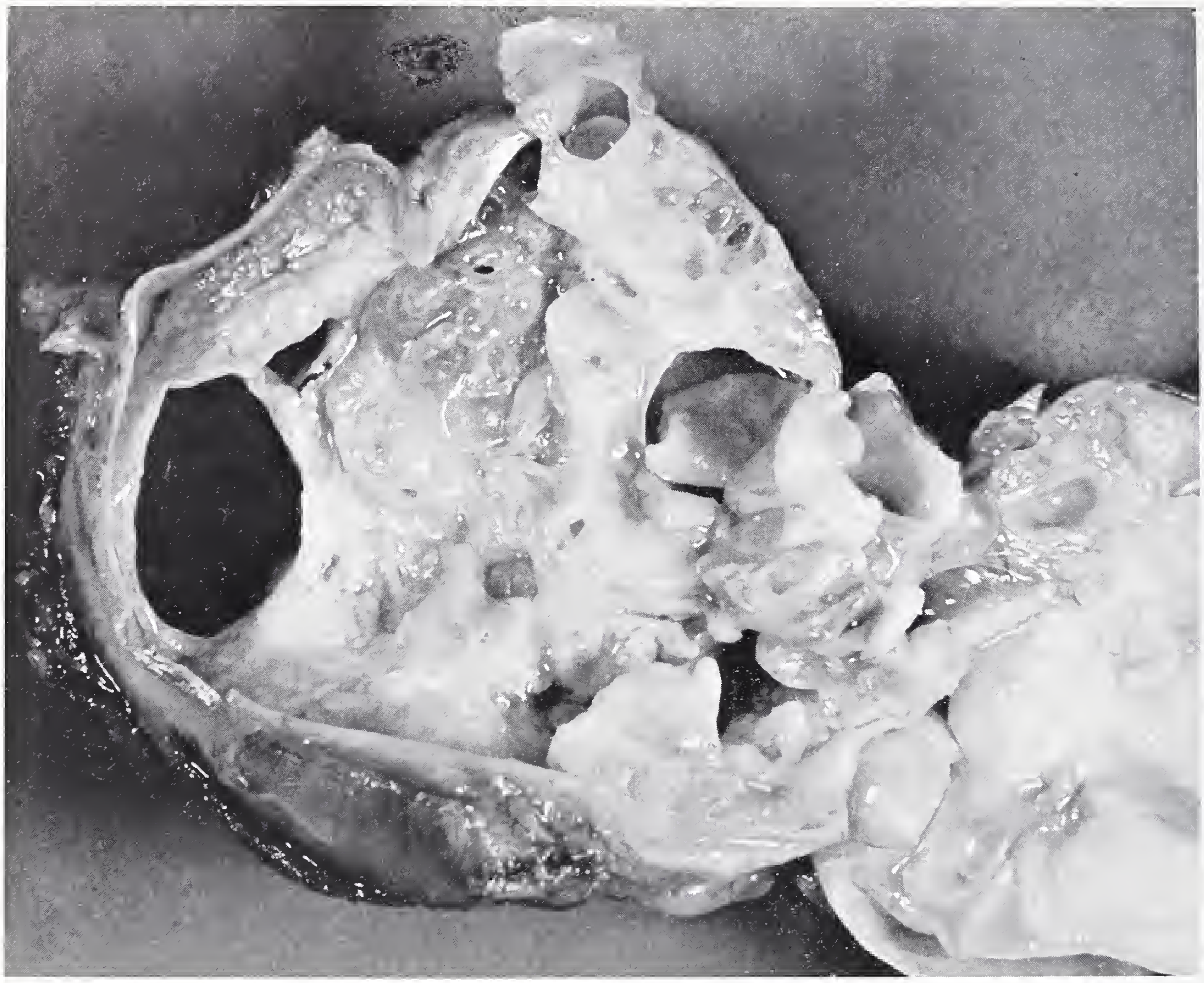

Figure 56
TERATOMA OF THE ORBIT
Deep portion of intraorbital teratoma showing the cystic and solid nature of the tumor (Courtesy of Dr. P. P. H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

differential diagnosis. Additional information relative to the pattern of growth, radiodensity, pulsatility, and spatial arrangement of the tumor tissue may be obtained from a systematic and comprehensive clinical and roentgenologic examination. Well known to pediatric oncologists is the tendency of some neuroblastomas to present as rapidly evolving exophthalmos. This may happen in the newborn period, but diagnostic investigation will disclose a primary neoplasm elsewhere in the body. A similar statement may be made with respect to lymphomas and leukemia; although these conditions have been known to present as problems in the differential diagnosis of exophthalmos in a young child, by the time the orbital contents are disturbed, enough evidence may be garnered from extraorbital sources to establish the correct diagnosis. Intraocular tumors, such as retinoblastoma, usually grow into the orbit only after their growth within the eye has been conspicuous. Nonneoplastic or inflammatory diseases should receive consideration, but the attending clinical circumstances, such as trauma or indications of infectious

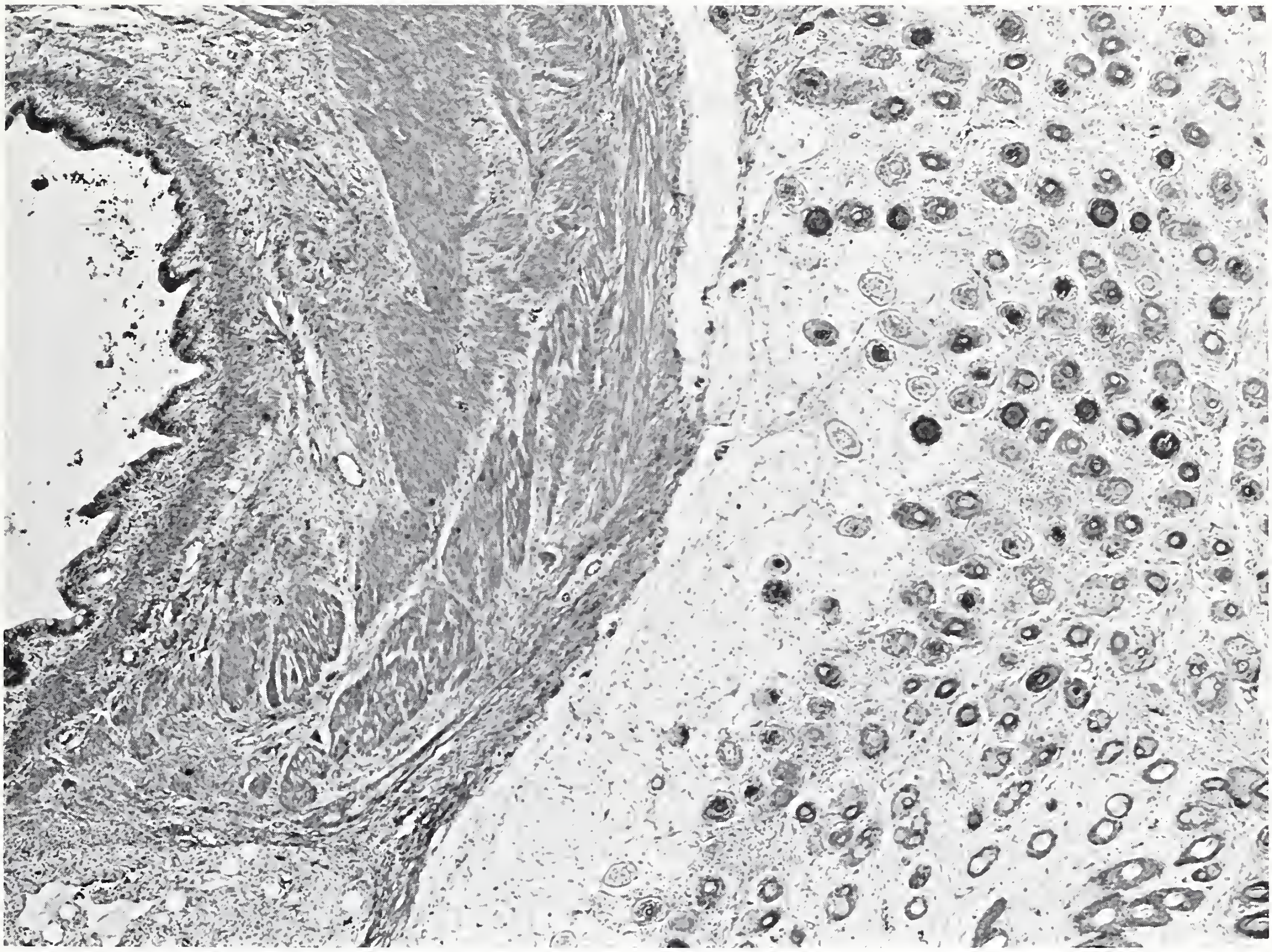

Figure 57
TERATOMA OF THE ORBIT
Well differentiated skin and intestinal tissues in the intraorbital teratoma. X65. (Courtesy of Dr. P.P.H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

disease, are apt to contribute toward elucidation of the problem. Malformative conditions, such as epidermal inclusion cysts, should present no serious problem of differential diagnosis once the specimen is examined in the laboratory.

Prognosis. With adequate and opportune care, the prognosis of children with intraorbital teratoma should be very good as to life. We know of no well documented case of metastasizing teratoma of the orbit, sporadic use of the epithet "malignant" notwithstanding (Saradarian). Unfortunately, the same optimism would be unfounded with respect to vision, as in most cases technical considerations have made enucleation mandatory (see Treatment). Children afflicted with intraorbital teratoma have been otherwise healthy, exception made of rare cases, such as that described in minute detail by Viana, in which the tumor penetrated the intracranial cavity and was associated with congenital hydrocephalus. This author thoroughly reviewed the older literature, and quoted a bizarre case described by Miuzo in which a tumor was punctured, and through the puncture wound was delivered what looked like a parasitic twin attached by an umbilical cord to the posterior part of the orbit.

Treatment. Sepsis was a common cause of death before the advent of modern antibiotic therapy and improved nursing care (Bartholdson et al.). Results are currently much better in spite of occasional accidents (Appalanarasayya and Devi), and the operations less mutilating than before, with preservation of periosteum and eyelids. Still, exenteration of the orbit has to be carried out in the majority of instances, owing to the retrobulbar position of the tumor, closely related to the optic nerve. Alkemade could find only four cases in which the eye could be saved due to the tumor being small and placed outside the muscular cone surrounding the optic nerve (Damato and Damato; Bröer and Weigert; Hoyt and Joe; Mortada). In one of these cases, the first in which the eye was spared (Girard et al.), the root of a cystic tumor measuring 4.5 cm. in greatest diameter was attached to the optic nerve, but could be dissected free. Reexamination of the patient one year postoperatively showed good extraocular muscle coordination and normal pupillary reaction to light stimulation. In the other cases, only slight adhesions have been present between the surface of the globe and the tumor (Damato and Damato), and no difficulties were encountered in delivering the tumor.

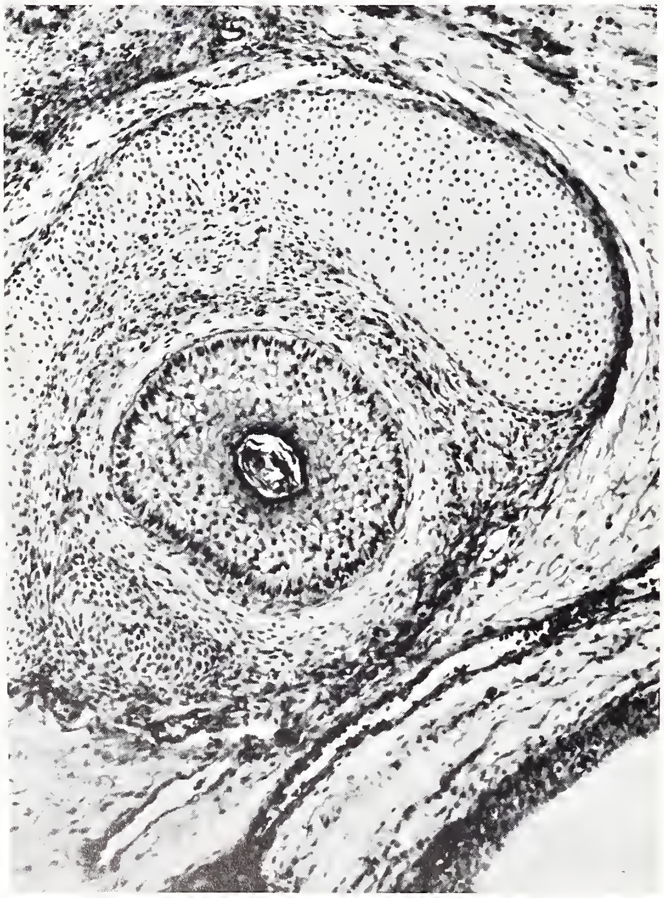

Figure 58
TERATOMA OF THE ORBIT
Island of cartilage in mesodermal portion of intraorbital teratoma. X115. (Courtesy of Dr. P. P. H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

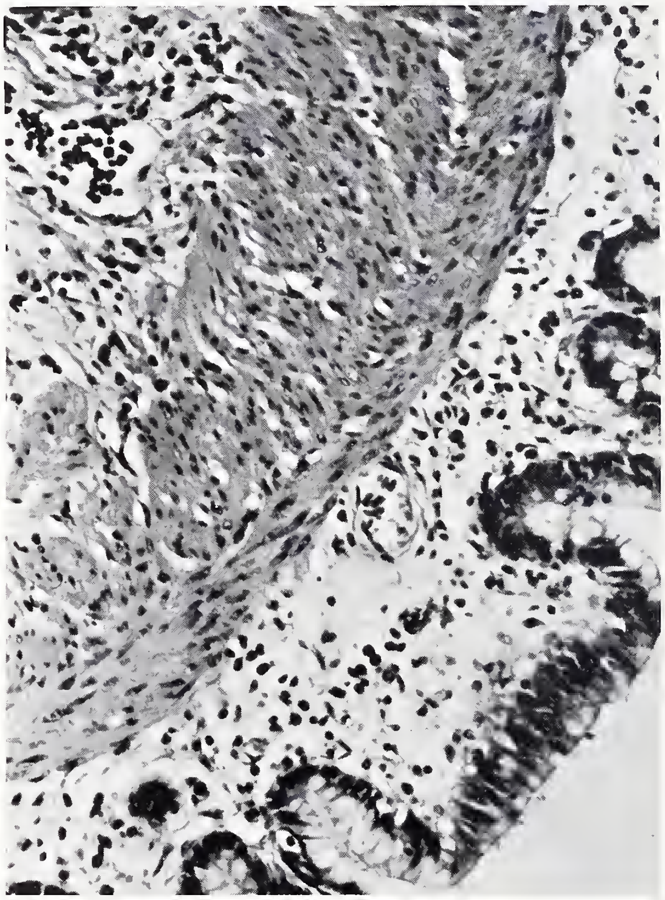

Figure 59
TERATOMA OF THE ORBIT
Alimentary tract tissues in congenital intraorbital teratoma. X425. (Courtesy of Dr. P.P.H. Alkemade, The Hague, Netherlands. From Congenital teratoma of the orbit. Ophthalmologica 173:274-285, 1976.)

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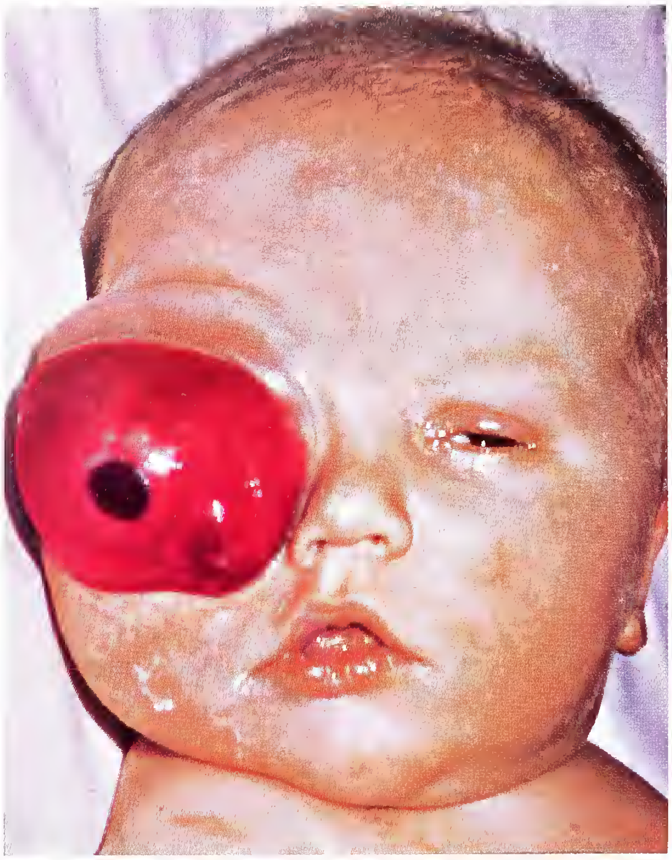
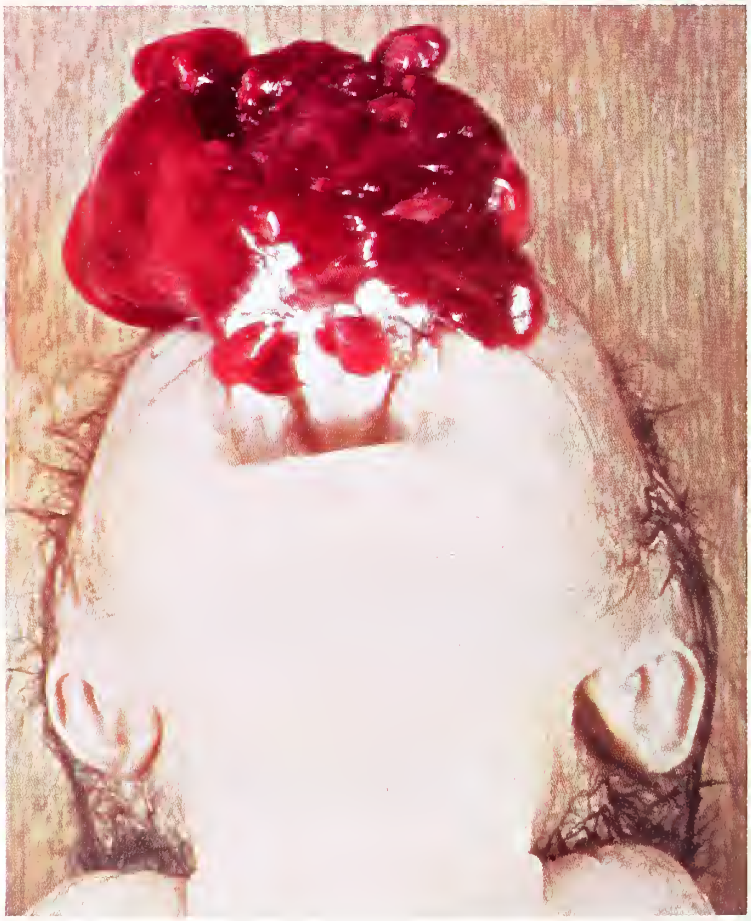
PLATE III



A. TERATOMA OF THE ORBIT

Congenital exophthalmos produced by intraorbital teratoma. In spite of rapid growth and shocking clinical appearance, these lesions are usually of low histologic grade and do not metastasize. The patient illustrated here is well 16 years after enucleation. Tumor excision with sparing of vision has been possible in a minority of cases.



B. BASICRANIAL TERATOMA

Large teratoma, so-called epignathus, arising from the palate in a newborn infant. Defect of closure of the palatal shelves is present at the tumor base. (Courtesy of Dr. L. David Mirkin, Indianapolis, IN.)

TERATOMAS OF THE HEAD (EXTRACRANIAL)

SYNONYMS AND RELATED TERMS: Epignathus; episphenoid; epipalatus; palatopagus; sphenopagus parasiticus; teratomatous choristoma; epuranus; basicranial teratoma; teratoma of the nasopharynx; teratoma of the mouth; teratoma of the palate.

In this section will be considered the rare teratomas arising in the face, oral and nasopharyngeal cavities, and base of the skull, exclusive of the upper cervical spine. The term "epignathus" is often used for teratomas originating in and around the oropharynx, although etymologically the word implies a relationship to the jaw.

The spectacular nature of many of these uncommon lesions attracted the attention of pathologists throughout the 19th century. In 1906, Schwalbe reviewed the subject and classified so-called epignathi into four classes. Class I he identified as a "parasitic monster" attached to the autosite through an umbilical cord; Class II, as an ill-defined tumor mass containing well developed organs and attached without cord interposition to either the head, neck, or thorax of the host. Class III presented the more conventional structure of teratoma with organized ectoderm, endoderm, and mesoderm tissue derivatives; Class IV was reserved for tumors of mixed tissue composition generally presenting as "hairy polyps" of the pharynx. Discussion of the nature of Schwalbe's Class I and Class II epignathi must be equated to the problem of abnormal twinning and its relationship to teratomas (see Hypotheses of Origin); at least some of these cases probably represent highly organized mature teratomas with gross features evocative of "fetiformity." "Umbilical cords" have been notably absent from cases of more recent vintage, and there is no definitive proof that these lesions represent conjoined twins. It has been hypothesized that the pluripotential cells giving rise to a teratoma of "epignathic" type occupy an area in the vicinity of Rathke's pouch and the oral membrane, at the point of contact of the buccopharyngeal membrane and the rostral end of the notochord. Wilson and Gehweiler noted the presence of an open canal into the cranial cavity in a patient with a facial teratoma. Presumably, neoplastic cell proliferation may start as early as the third week of gestation (Bruns), so that by the seventh to ninth weeks the tumor has grown to dimensions capable of interfering with the midline fusion of the palatal halves (Bennett; Bruns; Rintala and Ranta; Sollee). What the etiologic stimulus may be that brings about this neoplastic proliferation is currently unknown. Claims of enhanced vulnerability to tumorigenic influences of the tissue situated at the rostral end of the notochord (Agris et al.) are strictly hypothetical. Genetic interference with normal morphogenesis is suggested by the simultaneous occurrence of congenital anomalies outside the palatal area (Jover et al.), or by the occurrence of teratomas in association with chromosomal disorders. A teratoma of the internal auditory meatus was described in a male patient with 13-15 trisomy syndrome (Maniglia et al.); since detailed study of temporal bones is not a common practice in routine autopsy studies, it is impossible to know how frequently this association occurs. Similarly, we are aware of a case of oropharyngeal teratoma in a female anencephalic, but uncertain about the meaning of this association (fig. 60). A hypothesis that proposes the origin of teratomas as conjoined twins (see Hypotheses of Origin) predicts the mutual exclusion of these two conditions.

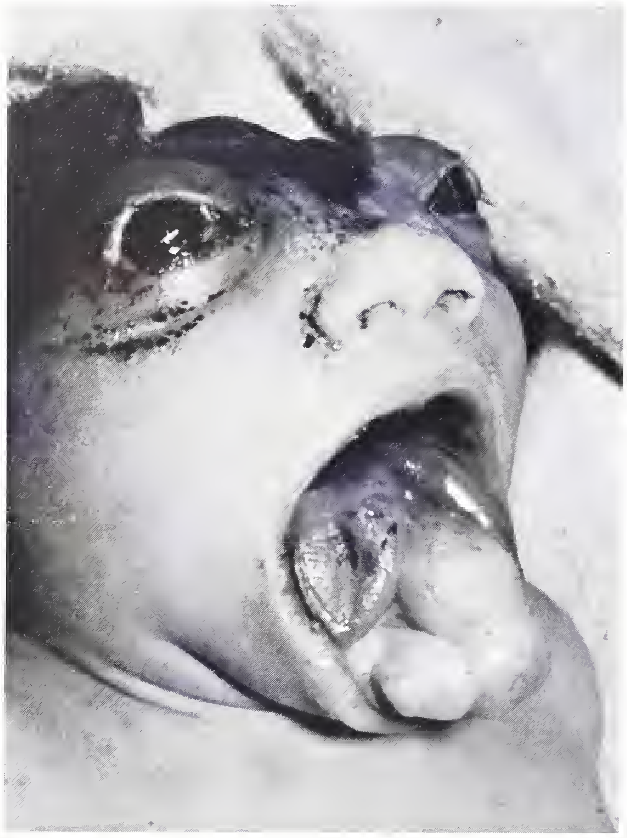


Figure 60
BASICRANIAL TERATOMA
Anencephalic female infant born with a teratoma of the oropharynx, protruding through the mouth. (Courtesy of Dr. C. Sotelo-Avila, Houston, TX.)

Clinical Features. The obvious manifestation of large tumors related to the facial orifices is airway obstruction. This may be life-jeopardizing, unless emergency tracheostomy is performed as a preliminary to corrective therapy. Upper alimentary tract obstruction may account for the associated hydraminos of some cases (Shapiro and Mix). A precise delineation of the way in which large basicranial teratomas may interfere with adequate prenatal development is not available. That this interference may be more complex than usually thought is suggested by the fact that most oral or nasopharyngeal teratomas result in death on delivery or during the neonatal period (Duckett and Claireaux), at times without clear correlation to the severity of neonatal asphyxia.

Congenital teratomas of the oral cavity commonly present as tissue masses projecting from the mouth (pl. III-B; figs. 60–62). Depending on the size of the tumor, there may be variable pressure deformities of the maxilla or mandible. Cleft palate is not uncommonly seen, especially at the attachment of the tumor (Shapiro and Mix; pl. III-B). The danger of infection in such cases is high; their anatomic localization introduces the risk of meningitis. When the tumor takes origin from the nasopharynx or para-

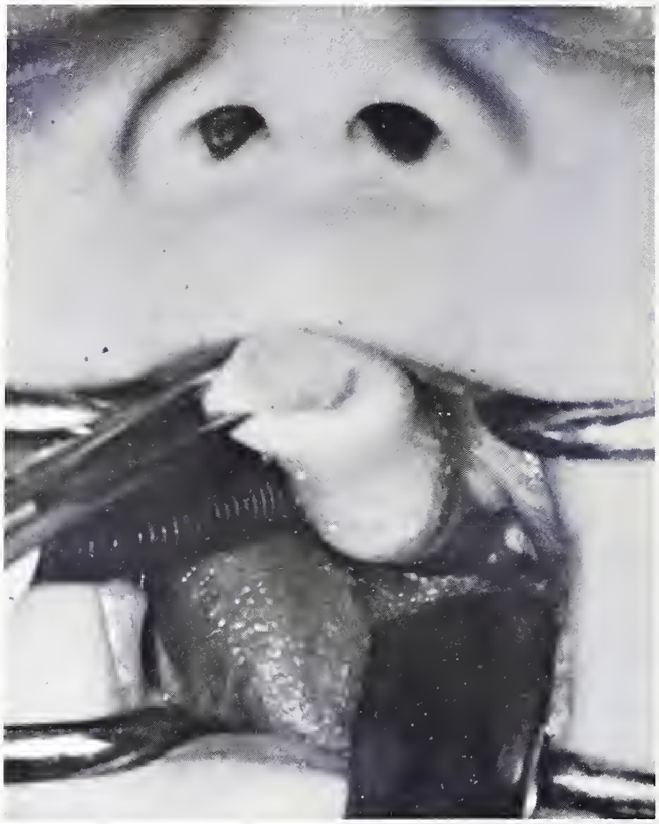


Figure 61
(Figures 61, 63, and 66 from same case)
BASICRANIAL TERATOMA
Congenital finger-like "hairy polyp" protruding from the nasopharynx. (Courtesy of Dr. Herman Felder, Pittsburgh, PA. From Felder, H. Benign congenital neoplasms: dermoids and teratomas. Arch. Otolaryngol. 101:333-334, 1975.)

nasal sinuses, the clinical manifestations may include ventilatory difficulties or epistaxis (Dicke and Gates). Interference with ventilation leading to fatal asphyxia is apt to occur in infants with nasopharyngeal teratoma. This may take place with small polypoid teratomas that do not extend into the mouth (Kesson; Raines and Yarington), or with the so-called hairy polyp, a pediculated, skin-covered lesion capable of occluding the upper airway (fig. 61), but whose tissue composition is less heterogeneous than that of teratomas and may thus represent a hamartoma. Smaller tumors have been described originating from the nasal septum (Tuson). In infants, the most common clinical manifestations of nasopharyngeal teratoma include respiratory distress, dysphagia, respiratory stridor, nasal hypersecretion, and palpable tumor protruding in the soft palate, less commonly into the oral cavity (Jover et al.; pl. III-B; figs. 60–62).

Teratomas of the temporal bone involving the middle ear were reviewed by Schuknecht in his scholarly monograph. This author illustrated a large teratoma of a 22 year old woman who had a postauricular prominence since early childhood. The tumor contained well differentiated tissues, including pancreas with islets of Langerhans. No mention was made of histologic

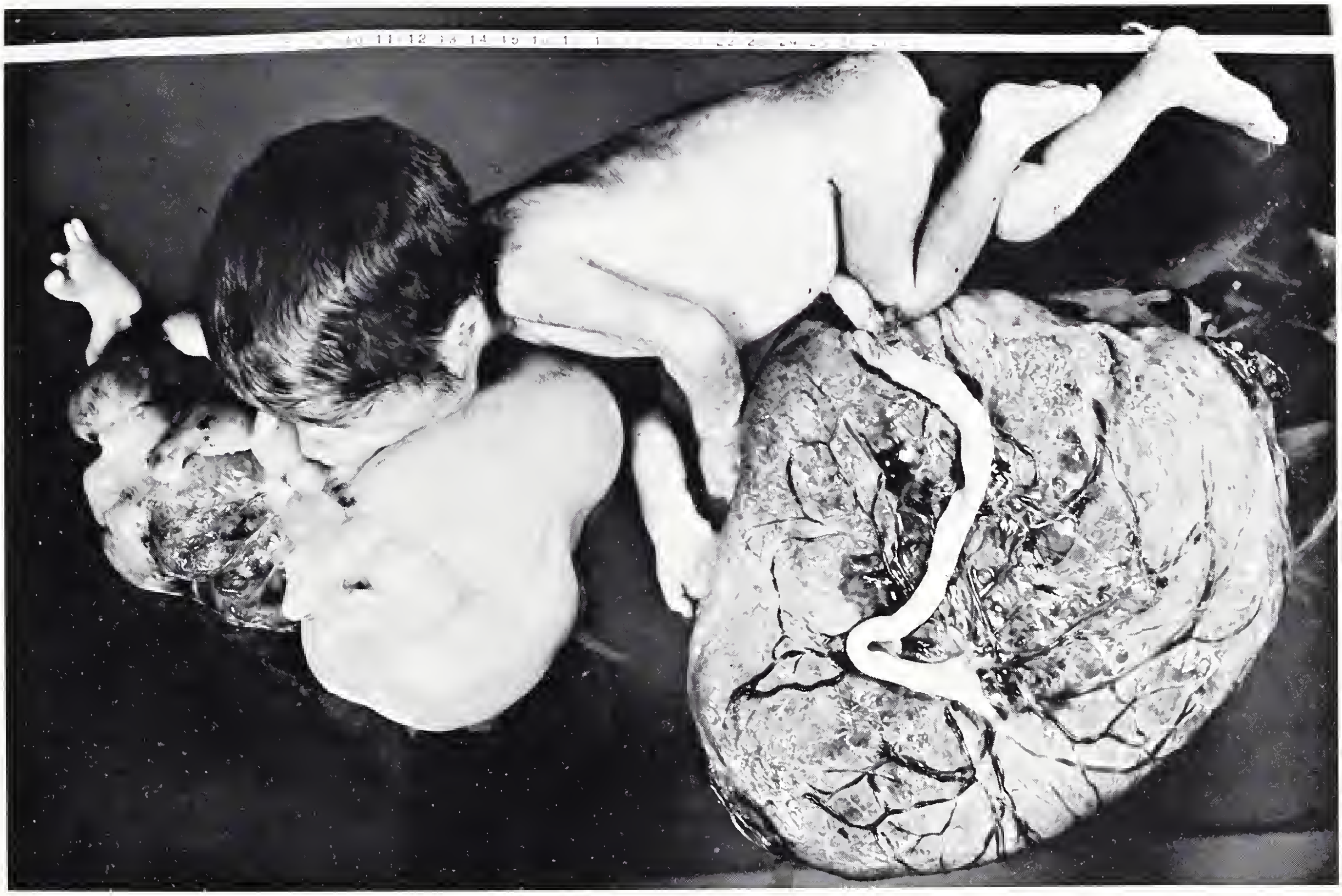


Figure 62
(Figures 62 and 64 from same case)
BASICRANIAL TERATOMA
Large "epignathic" teratoma in a newborn infant. The tumor shows features strongly suggestive of a deformed parasitic twin. (Courtesy of Dr. J. M. Kissane, St. Louis, MO.)

malignancy in teratomas of eustachian tube or temporal-mastoid localization. Within the oropharynx, the origin of teratomas has also been traced to the tonsil. Ten such cases were recently reviewed by Shah and associates.

Isolated teratomas arising from the tongue are rarities, but should be included with other lesions of "epignathic" type. Two such examples have been described in detail (Bras et al.; Miller and Owens). Both were congenital lesions covered by lingual mucosa, arising in otherwise normal infants, and presenting as pedunculated growths attached to the lateral aspect of the tongue. Histologically, both tumors were benign, one predominantly gliomatous (Bras et al.); excision was curative. In one case, a 5-year follow-up examination disclosed no abnormalities (Miller and Owens).

Roentgenologic and Laboratory Examination. Radiographs of the skull and pneumoencephalogram are often indispensable to rule out the possibility of communication between the basicranial tumors and the subarachnoid space. The base of the skull and the cranial vault frequently appear normal in benign cases (Agris et al.), and calcification deposits within the tumor parenchyma are not uncommon. Thorough roentgenologic examination, however, may disclose associated anomalies, such as vertebral deformities (Rintala and Ranta), cleft palate, or secondary displacement of normal structures. The absence of calcifications does not rule out the teratomatous nature of the mass (Gifford and MacCollum; fig. 63). Areas of calcification or ossification alternate with zones of diminished radiodensity, frequently interpreted as representing fat, and other dense areas suggestive of cartilage. The variegated radiographic appearance may suggest a teratoma even in atypical or infrequent locations (Wilson and Gehweiler). Ultrasound technics offer the potential for more frequent prenatal diagnosis of this condition.

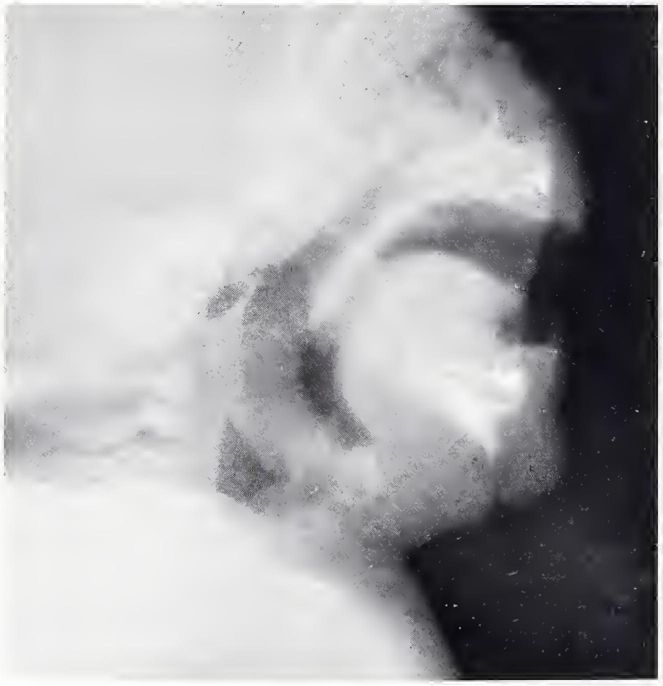


Figure 63
BASICRANIAL TERATOMA
Roentgenologic appearance of nasopharyngeal "hairy polyp" extending into the hypopharynx. (Courtesy of Dr. Herman Felder, Pittsburgh, PA. From Felder, H. Benign congenital neoplasms: dermoids and teratomas. Arch. Otolaryngol. 101:333-334, 1975.)

Gross Appearance. In their original location, intraoral teratomas are frequently described as pediculated masses composed of gelatinous tissue, often with finger-like projections, bony elements, and tooth buds, and ordinarily large enough to displace the tongue and other normal formations. Although the tumor stalk may appear narrow, not uncommonly additional tumor tissue spreads cephalad or posteriorly, toward the nasopharynx. The tumors may attach to the roof of the pharynx, palate, maxillary bone, or investing mucosa (Chew and Teoh; pl. III-B; figs. 60–64). The base of the skull need not be affected in the larger examples with exophytic growth; however, some of these tumors present an "hourglass" shape with an intracranial extension. At least three cases are on record in which a teratoma projecting from the mouth was associated with an intracranial teratoma (Breslau and Rindfleisch; Duckett and Claireaux; Greenhouse and Neubuerger). This may occur in the form of intraoral extensions of a teratoma purportedly arising in the vicinity of the pituitary gland, or, as in the case of Duckett and Claireaux, as two separate tumors without any anatomic connection. Multiple teratomas can rarely be present simultaneously in the head and neck. In one such case, a right submandibular cystic teratoma coexisted with a second teratoma of the right lateral aspect of the tongue (Dudgeon et al.). Separate teratomas of the mandible and nasopharynx have also been seen in the same patient (Rintala and Ranta). As stated precedingly, some tumors of the "epignathic" type may exhibit striking organ development; when recognizable limb development is present, it is usually of the distal limb portions (figs. 62, 64).

Microscopic Appearance. Teratomas of oral and mandibular origin usually display prominent tooth germs histologically. In some instances, this may represent displaced odontogenic tissue normal to this anatomic area. The teratomatous nature of these lesions, however, is made apparent by the presence of skin, hair, sebaceous glands, and other tissue components foreign to the site (Rintala and Ranta). Ependymal cells forming rosettes, intestinal mucosa, eye structures (Duckett and Claireaux; Tuson), muscle, bone, and cartilage are mentioned in case reports (figs. 65–67). Skin-covered pedunculated masses, referred to as "hairy polyps," may protrude into the pharynx; their surface is lined by stratified squamous epithelium overlying a central core that contains numerous skin appendages, cartilage rods, and other mesenchymal derivatives (fig. 66). Tissue differentiation is restricted, and it is likely that such lesions are best grouped with hamartomas. Larger tumors are commonly multilobulated; the multiplicity of tissue composition is entirely comparable to that of teratomas of other sites. Definitely malignant tissues have not been identified in basicranial teratomas present at birth.

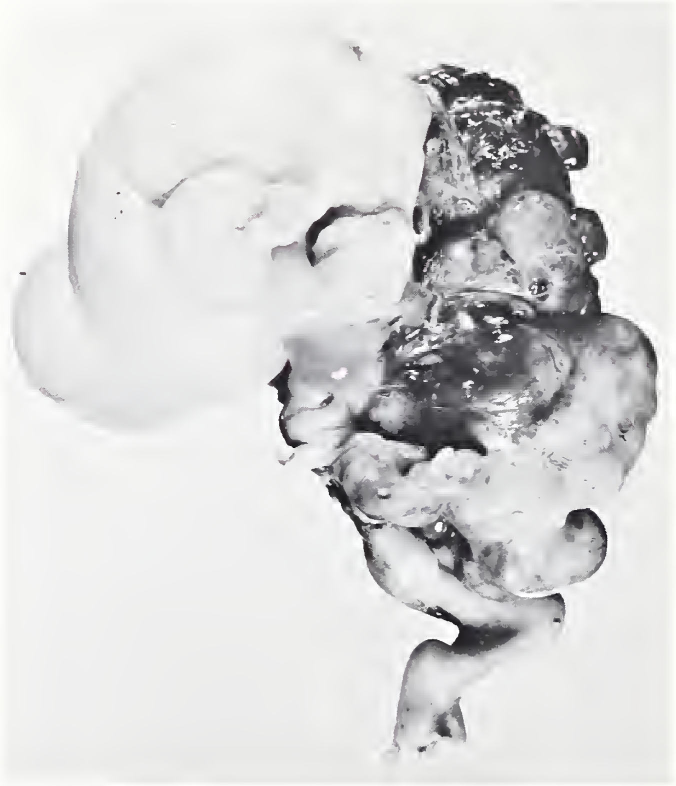


Figure 64
BASICRANIAL TERATOMA
Multilobulated teratoma of figure 62 shows evidence of limb development. This tumor, however, lacks formation of a vertebral axis. (Courtesy of Dr. J.M. Kissane, St. Louis, MO.)

Differential Diagnosis. A clinical dictum exhorts to regard all polypoid intranasal masses as brain herniation until proved otherwise (Weaver et al.). Such an attitude may be justifiably extended to all basicranial masses, especially cystic ones. Terms such as "encephaloma" (Browder), "brain heterotopia" (Orkin and Fisher), "neuroglial heterotopia" (Bratton and Robinson), or encephalocele, designate a group of lesions characterized by mature brain tissue components occurring outside of the cranial cavity. The best known type is the so-called nasal glioma (Bratton and Robinson; Kubo et al.). Resemblance of these lesions to true teratomas may be due to the presence, in the former growths, of a variety of cells, including astrocytes, oligodendroglia, primitive retina (Shapiro and Mix), and papillary excrescences usually interpreted as choroid plexus. All these lesions, however, are maldevelopmental rather than neoplastic, and, as such, lack an intrinsic potential for autonomous growth.

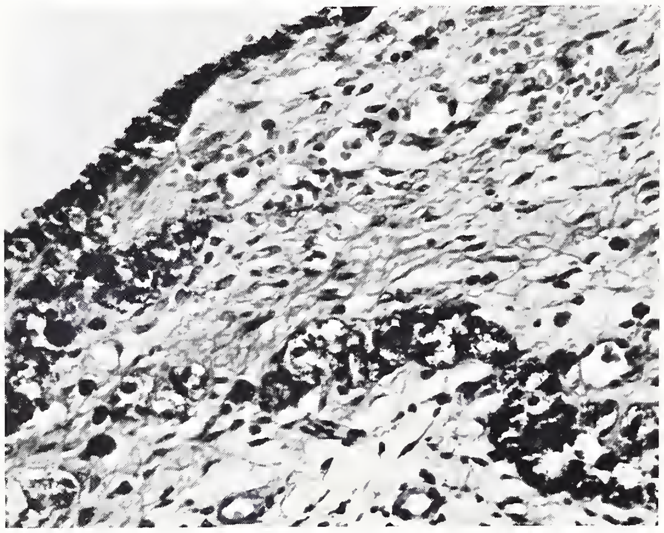


Figure 65
BASICRANIAL TERATOMA
Melanin-containing cells reproduce the structure of the ocular iris in oropharyngeal teratoma. X125.

The maxilla of young children may be the site of origin of the lesion known as pigmented neuroectodermal tumor of infancy. This neoplasm should be included in the differential diagnosis of teratomas because it is often diagnosed before one year of age, tends to occur in a variety of locations, especially skull and jawbones, and presents a composite microscopic appearance of tissues foreign to the site of origin. It is characterized by the presence of small melanin-containing cells set in a fibrous or myxoid stroma. Attempts at organ formation are not seen, and the endodermal derivatives are not an integral part of pigmented neuroectodermal tumor, which is considered to derive from neural crest cells. Foci of pigmented neuroectodermal tumor have been seen in a case of glial heterotopia arising in the oropharynx (Lee et al.). Most heterotopias of neural tissues are readily distinguished from teratomas, however, by the exclusively ectodermal derivation of the "displaced" or aberrant tissues.

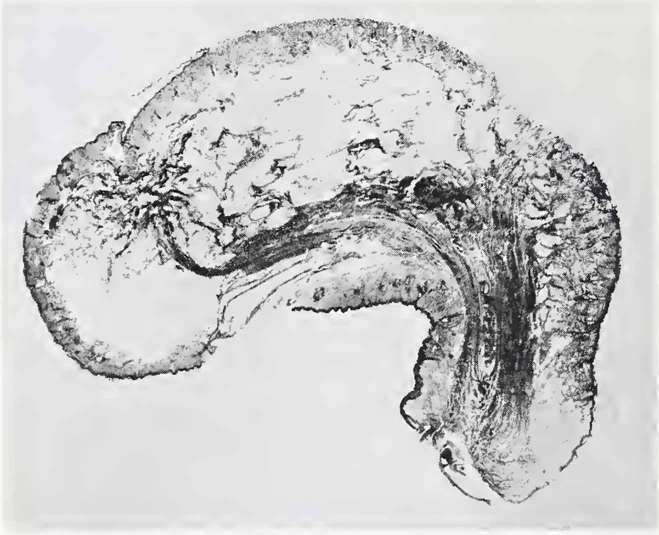


Figure 66
BASICRANIAL TERATOMA
Microscopic appearance of polypoid nasopharyngeal teratoma shown in figures 61 and 63. Central core contains abundant striated muscle. Surface is covered by skin. Original magnification X1.5. (Courtesy of Dr. Herman Felder, Pittsburgh, PA. From Felder, H. Benign congenital neoplasms: dermoids and teratomas. Arch. Otolaryngol. 101:333-334, 1975.)

Heterotopic neuroectodermal tissues may arise in the oropharynx (Browder; Lee et al.) or palate (Shapiro and Mix) and adopt a pedunculated gross appearance that likens them to tumors of the "hairy polyp" type; morphologic distinction from a teratoma rests in the purely ectodermal differentiation of the former. True tumors arising from the olfactory membrane that subsequently display a strong propensity for intracranial dissemination, most often correspond to olfactory neuroblastoma (Robinson and Solitare); differential diagnosis from a teratoma is not a problem in these lesions.

Intraoral cysts of maldevelopmental nature also occur. These may take the form of intraoral cysts lined by ectopic gastrointestinal mucosa (Brown and Kerr-Wilson) or squamous mucosa and should therefore be distinguished from a cystic teratoma. Duplication cysts may originate from the tongue or the walls of the mouth, but do not have the composite histologic appearance of a true teratoma.

Prognosis. Despite the lack of well documented histologic malignancy, congenital teratomas of the oral and nasopharyngeal cavity are frequently associated with a lethal clinical course. Rintala and Ranta found reports of only six cases successfully excised up to 1974. However, even massive teratomas of this site have been cured after appropriate surgical management. Long-term survival has been possible following treatment of large teratomas projecting from the mouth, without intracranial involvement (Bennett). Dohlman and Sjövall reported a successfully treated patient who was well more than seven years after the operation.

Malignant teratomas primary of the

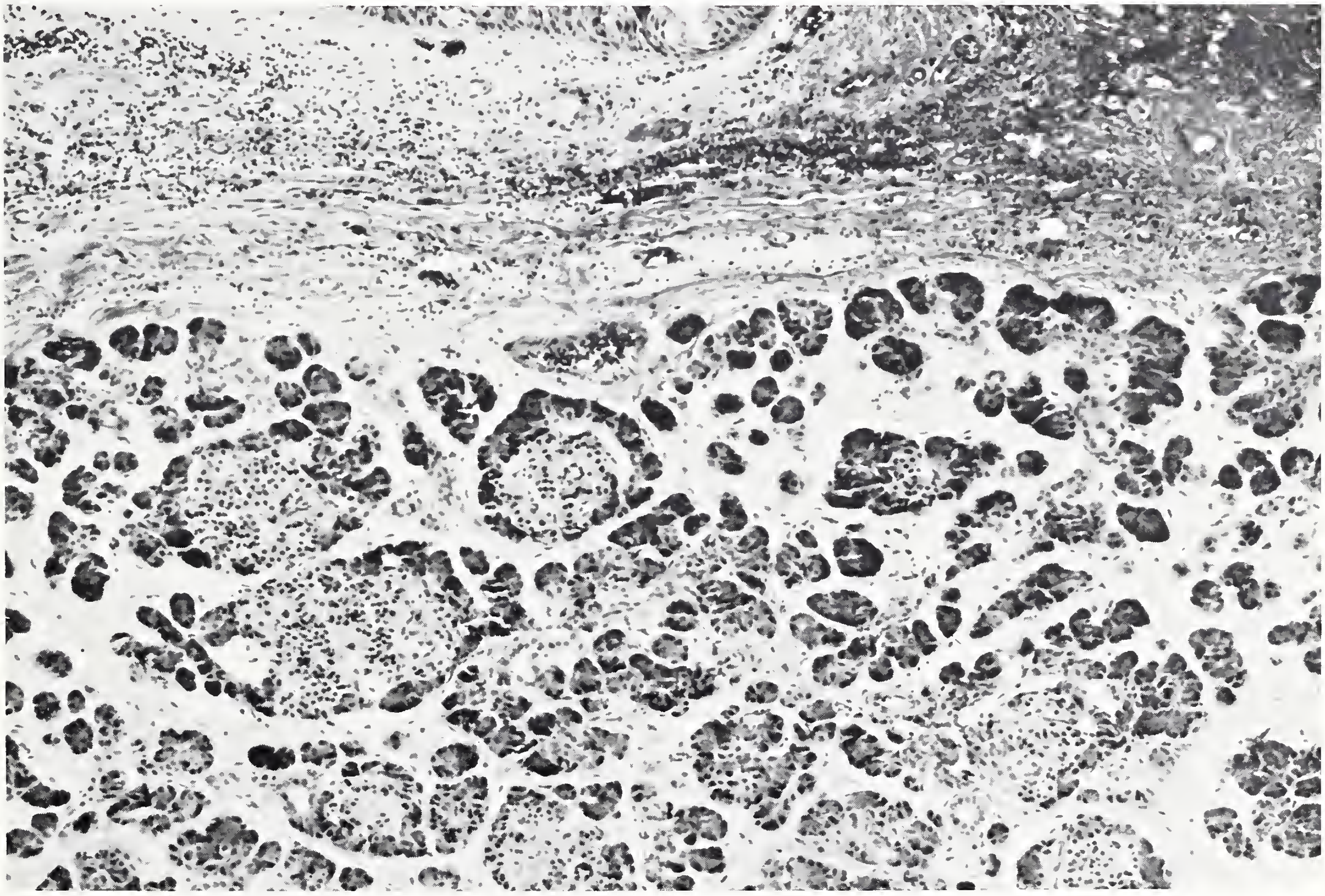


Figure 67
BASICRANIAL TERATOMA
Mature benign teratoma of the tongue in which there has been differentiation to pancreatic tissue with islets of Langerhans. X270.

nasopharynx are extremely rare. Patchefsky and co-workers, and Dicke and Gates have described isolated tumors that were called primary malignant teratoma of the paranasal sinuses. The tumors became manifest in adult patients, initially with deceptively innocuous symptoms of nasal stuffiness and epistaxis. These neoplasms contained an admixture of mature glandular and squamous epithelial elements with focal areas of immature neurogenic cells resembling neuroblastoma, ependymoma, and esthesioneuroepithelioma. Because of the exceptional nature of these cases, attribution of a teratomatous origin must be considered tentative.

It appears, thus, that the important prognostic determinants are: the age of presentation; the nature of the technical problems associated with removal of a neoplasm situated in an area of difficult access; the associated anomalies and complications; and the nature of the tissues composing the teratoma.

Treatment. Total excision is the therapeutic procedure of choice. Local recurrences have been observed after removal of teratomas of the mouth of benign histologic composition (Keswani et al.). It is likely that this occurrence represents residual growth of neoplasms incompletely excised. It cannot be overemphasized that a satisfactory treatment is largely subordinate to highly specialized and skillful anesthetic and nursing management. Opportune intervention to maintain an open airway should be of primary concern. Tracheostomy may be necessary, especially with the very large and sessile nasopharyngeal masses, whose complete removal would be otherwise difficult or incomplete. Preanesthetic aspiration of fluid may be indicated if the mass is largely cystic and there is danger of asphyxiation (Paul and Arora).

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◆

TERATOMAS OF THE NECK

SYNONYMS AND RELATED TERMS: Cervical teratoma; thyroid teratoma; tridermal teratoma of the cervical region; fetal teratoma of the neck; teratoma of the thyroid region.

Teratomas arising in the neck are uncommon. Pooling the cases of teratoma of infancy and childhood reported in four major series (Bale; Berry et al.; Carney et al.; Grosfeld et al.), only 16 of 335 teratomas, or 4.7 percent, were in the neck. Hajdu and associates attributed the first well documented report of a cervical teratoma to Hess, in 1854. A century later, less than 100 cases had been reported (Silberman and Mendelson).

The term "cervical teratoma" generally incorporates lesions arising in the anterior and posterior triangles of the neck to the exclusion of those involving the base of the skull and the cervical spine. Attempts to subclassify teratomas of the neck into thyroid teratomas and cervical, or extrathyroid, teratomas (Silberman and Mendelson), on the basis of their blood supply, are not warranted. Moreover, in most cases it is difficult to determine the origin of the main feeding vessels. One of the outstanding characteristics of teratomas originating anteriorly in the neck is that a relationship with the thyroid can be discovered in the majority of cases. This may be actual replacement of thyroid parenchyma, involvement by direct continuity, or intimate attachment of the tumor to the gland's capsule. This relationship is so constant that Roediger and associates have been able to argue persuasively that all teratomas presenting in the anterior neck region arise from embryonic cells in the primitive anlage of the thyroid gland. In the rare instances in which muscle and soft tissue are interposed, this may be due, in their opinion, to mechanical dislocation of embryonic teratogenic cells in a manner analogous to the dislocation of normal thyroid tissue that comes to lie adjacent to, and at some distance from, the normal gland (Bale; Silberman and Mendelson). Other authors do not share this opinion and regard the relationship with the gland as entirely fortuitous (Colton et al.), in view of extreme rarity of intrathyroid origin.

There is no satisfactory explanation for the development of these tumors. To our knowledge, a single report of congenital cervical teratoma occurring in siblings has appeared (Hurlbut et al.). The mother of these infants had no evidence of thyroid disease and received no medication during pregnancy. Births took place 10 years apart. No evidence of recurrence was observed upon reexamination of the first child, 10 years after resection. Colton and co-workers reviewed the literature on teratomas of the neck in adults in 1978, and found a total of 10 cases.

Clinical Features. In the vast majority of cases the tumor presents clinically as a large oval mass in the neck, noted at birth (figs. 68–70). The consistency of the mass usually reflects the partly cystic and partly solid nature of most teratomas. There is no predilection for left, right, or median regions of the neck. All races and both sexes are affected with approximately equal frequency (Grosfeld et al.; Silberman and Mendelson).

The largest tumors may extend in a cranial direction up to the mastoid process, and caudad to the clavicle. With such large masses, the neck of the unborn child may be hyperextended, thus predisposing to dystocia at the time of delivery; the volume of the tumor may be sufficient to cause obstetrical difficulties. Teratomas that grow to these large dimensions are apt to produce tracheal deviation (fig. 71) and compression of the esophagus. An important consequence is the development of hydramnios, a complication that is described in approximately one-third of the reported cervical teratomas. The mechanism of hydramnios is the same as in congenital obstruction of the upper gastrointestinal tract due to intrinsic malformation, namely, interference with deglutition of the amniotic fluid (Rosenfeld et al.).

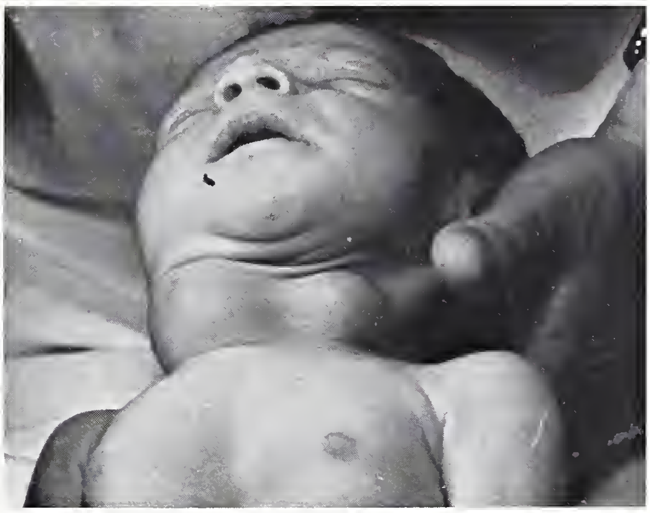

Figure 68
CERVICAL TERATOMA
Congenital teratoma of the neck causing enlargement of both thryoid lobes. (Courtesy of Dr. C. Sotelo-Avila, Houston, TX.)

Hajdu and associates found a direct correlation between the size of the teratoma and the development of hydramnios: when the tumor exceeded 10 cm. in greatest diameter, hydramnios was almost always found. This finding has been present in association with a 5 cm. cervical teratoma (Rosenfeld et al.). Except for hydramnios, the maternal history is generally unremarkable. Neither the number of previous pregnancies nor a history of previous obstetrical difficulties seem to correlate significantly with these tumors. The intrauterine effects of the teratoma are poorly known. That they may be clinically important is suggested by the fact that 17 percent of infants with congenital teratoma are stillborn (Hajdu et al.; Pupovac; Silberman and Mendelson). On the other hand, most reports fail to mention the presence of clinically significant associated conditions in patients with cervical teratoma, and it is assumed that the presence of the tumor accounts for the mortality.

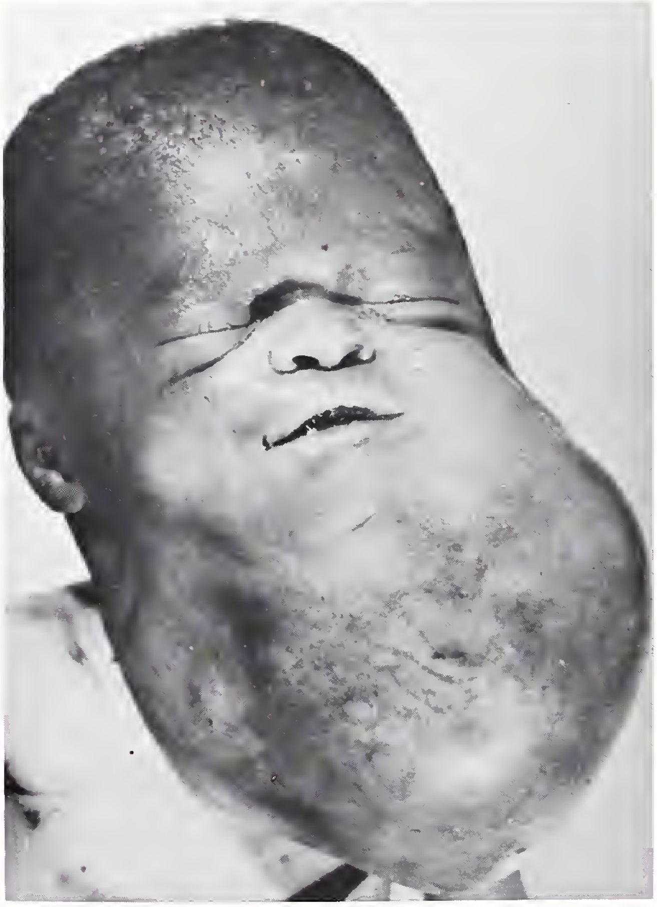

Figure 69
CERVICAL TERATOMA
Massive congenital teratoma presenting as an anterior neck mass in an infant whose gestation was complicated by hydramnios. (Courtesy of Dr. Steven I. Hajdu, New York, NY. From Hajdu, S. I., Faruque, A. A., Hajdu, E. O., and Morgan, W. S. Teratoma of the neck in infants. Am. J. Dis. Child. 111:412-416, 1966.)

"Chondrodystrophic" dwarfism with rhizomelia was illustrated by McGoon in a newborn infant with cervical teratoma. Conditions causing upper gastrointestinal obstruction during fetal life are well known to cause various degrees of hypoplasia of the distal "unused" portions of the alimentary tract. No documentation of such an effect has been provided in patients with congenital cervical teratoma.

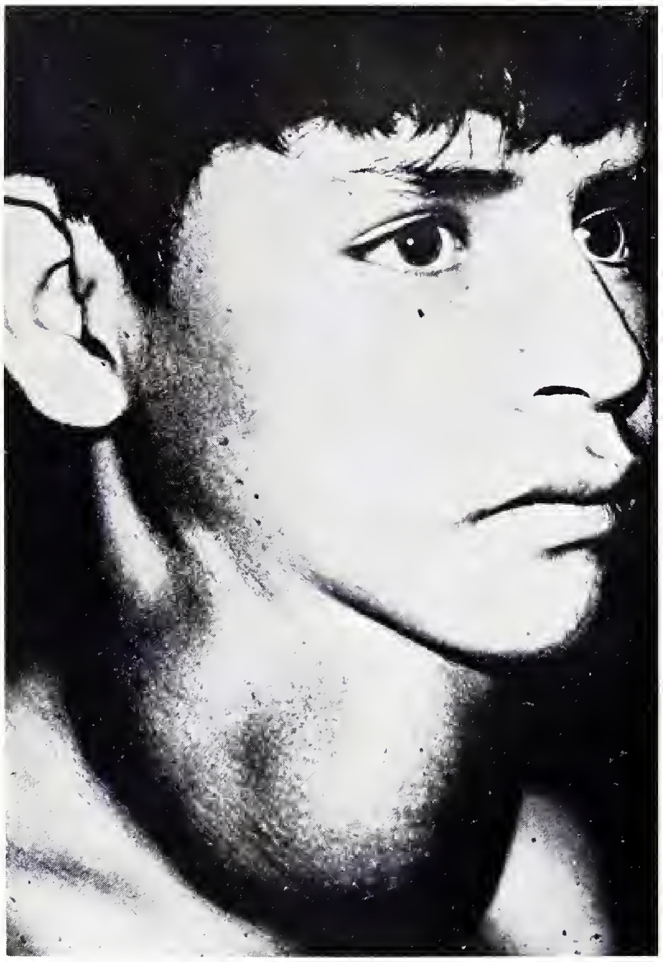

Figure 70
(Figures 70 and 72 from same case)
CERVICAL TERATOMA
Teratoma of the neck in a 13 year old adolescent. The tumor was present since birth, and grew gradually. (Courtesy of Dr. J. Albores-Saavedra, Mexico City, Mexico.)

Teratomas of the neck have been discovered in adults. The patients have been between 23 and 85 years of age, and symptoms have been present for a long time: in one case, for up to 50 years (Kemp). Rarely, adolescents may be affected (fig. 70). Seven out of 10 cases reported in adults have been said to be histologically and clinically malignant, but the type of malignancy has been poorly described. In the tumor described by Colton and co-workers, the malignant elements were neuroectoderm and poorly differentiated carcinoma.

Roentgenologic and Laboratory Examination. In very few cases has the function of the thyroid gland been studied. Cruz Ortiz and associates were able to determine that in one case of teratoma of the thyroid in an adolescent, the uninvolved gland showed some iodine uptake, and normal formation and release of thyroid hormones. The radiologic appearance is not diagnostic (figs. 71, 72); as in other teratomas, characteristic calcifications may be seen. A combination of sonography and amniography has been used to demonstrate proximal gastrointestinal obstruction prenatally (Rosenfeld et al.). Failure to visualize contrast media in the gastrointestinal tract 12 hours after injection of this material in the amniotic cavity indicates either failure of deglutition or anatomic obstruction; in either case, the pediatrician should be alerted. Sonography has demonstrated prenatal tumors, but missed a cervical teratoma reported by Rosenfeld and coworkers.

Gross Appearance. These tumors most commonly appear as spherical or ovoid masses, often well encapsulated, and distinctly irregular or lobulated at their outer surface. The cut surface shows variable cystic components, and firm fibrous solid areas, in which cartilage may be seen. Organ formation may be striking (pl. IV-A). A case is on record in which the tumor grossly resembled a complete fetus with rudimentary limbs, trunk, one eye, and ear tubercles on a head covered with hair (Chandak et al.). This case, however, showed no skeletal organization, and, microscopically, the tissues were assembled in marked disarray; "fetiformity" was purely external and true organ formation did not exist.

Microscopic Appearance. The majority of these tumors have appeared benign on pathologic examination. The first description in the English language of a malignant teratoma in the region of the thyroid gland, is that of Buckwalter and Layton. The patient was a 29 year old woman, and the tumor contained embryonic appearing areas of primitive mesenchyme, as well as neuroectodermal tissue with formation of tubular structures. These tissues were clearly invasive, and of rapid growth. The patient succumbed with radiologic evidence of pulmonary metastases, but an autopsy was not performed. Other cases have been called malignant on the basis of similar histologic findings, but without adequate follow-up. Older descriptions exist in the German literature that have documented lymph node metastases (Fritzsche; Lurje; Pupovac), but it is difficult to be certain of the microscopic appearance of the neoplasm, and how it may relate to present-day classifications. The benign cases have shown a great variety of tissue components (figs. 73–77). Glial elements resembling "brain tissue" and thyroid gland components are possibly the most commonly found tissues in cervical teratomas (Saphir).

According to Colton and associates, teratomas of the neck in childhood tend to be

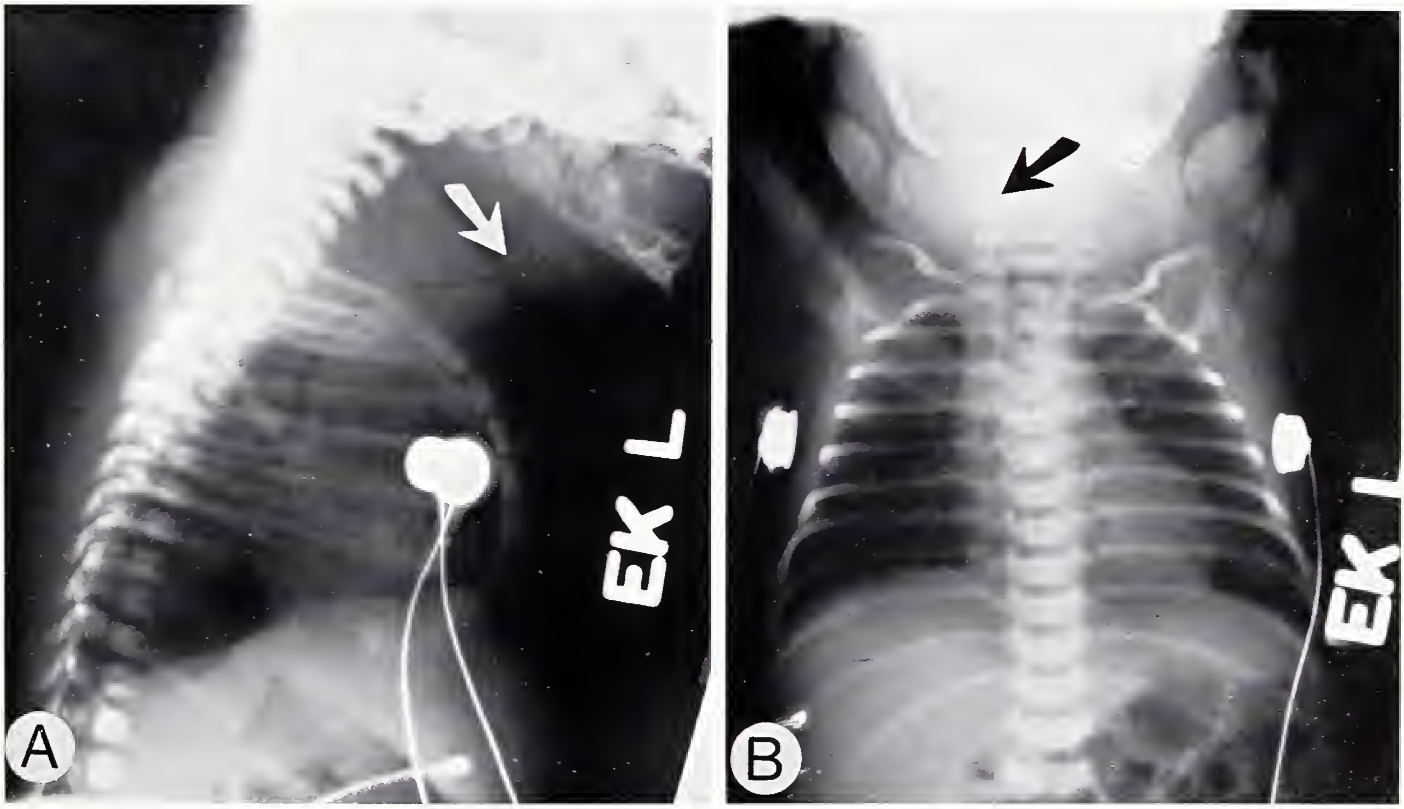

Figure 71
CERVICAL TERATOMA
Lateral (A) and anteroposterior (B) views demonstrate marked tracheal deviation in a newborn with a congenital anterior cervical teratoma. Arrows point to the endotracheal tube. (From Rosenfeld, C. R., Coln, C. D., and Duenhoelter, J. H. Fetal cervical teratoma as a cause of polyhydramnios. Pediatrics 64:176-179, 1979.)

well differentiated histologically and behave in a benign fashion clinically, whereas those of adult patients are generally malignant. They stated that cervical teratomas in adult patients may exhibit a sarcomatous or a carcinomatous pattern. However, the cervical teratomas with purportedly malignant behavior have been composed of immature, embryonic tissues (Pilheu et al.).

Differential Diagnosis. Clinically, the principal differential diagnoses include cystic hygroma, branchiogenous cysts, and thyroglossal duct cyst. All these lesions present as soft masses in the neck of infants and children, and are considerably more common than the rare cervical teratoma.

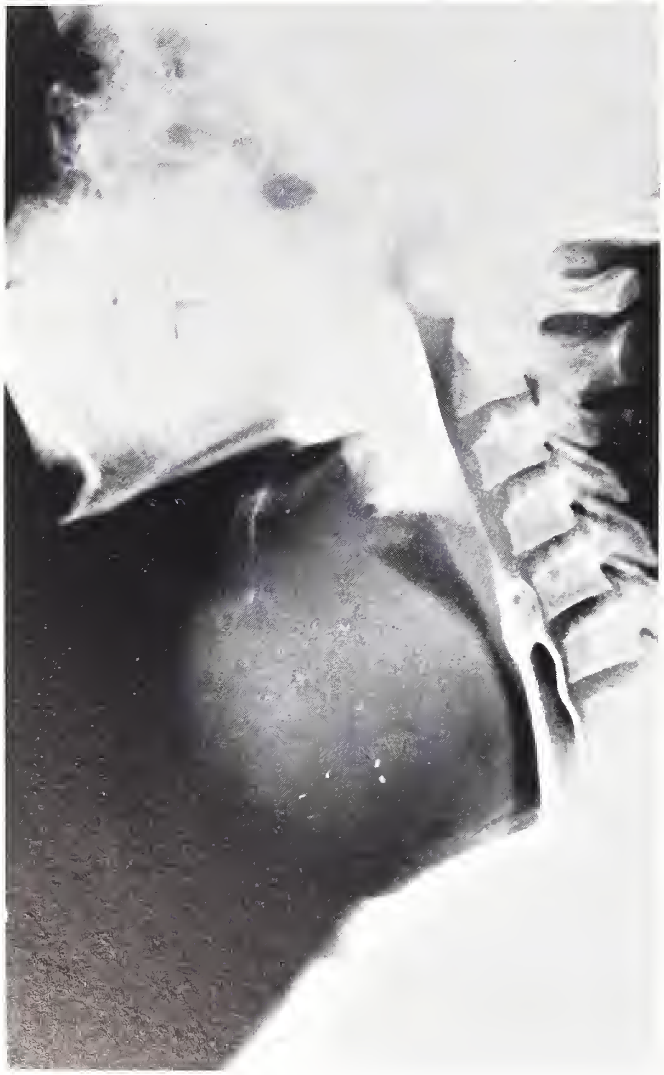

Figure 72
CERVICAL TERATOMA
Lateral roentgenogram of the neck (same case as fig, 70). Homogeneous mass with scattered calcifications causing only minimal tracheal compression and no significant esophageal alteration. (Courtesy of Dr. J. Albores-Saavedra, Mexico City, Mexico.)

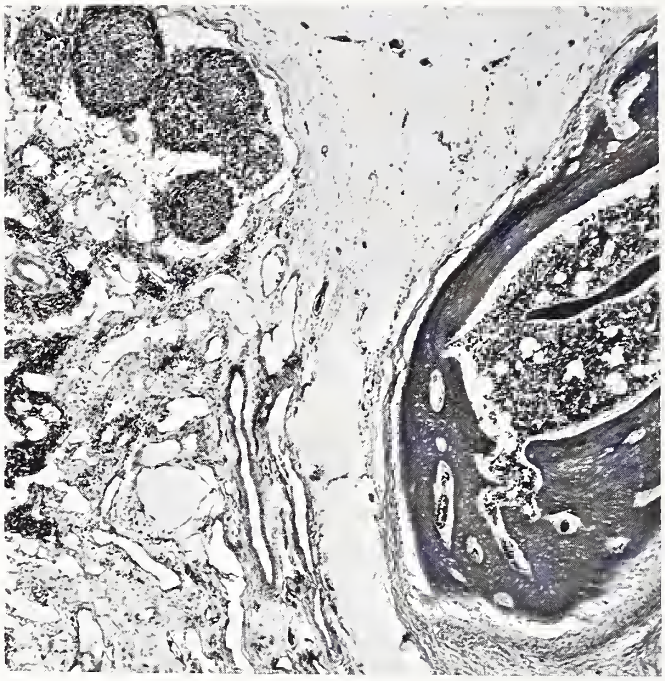

Figure 73
(Figures 73–77 and plate IV-A from same case)
CERVICAL TERATOMA
Well formed lymph node (left) adjacent to mature bone containing normal bone marrow (right) in cervical teratoma with organoid differentiation. X125.

Cystic hygroma is an infrequent lesion appearing as a fluctuant mass in the posterior triangle of the neck, occasionally extending beneath the clavicle into the axilla. Only a few lesions are seen in the anterior cervical triangle, and then high in the submandibular area. Most patients are asymptomatic, and the tumors readily transilluminate. Location, consistency, lack of symptoms, congenital nature, and appearance on transillumination are generally so characteristic that a serious problem of differential diagnosis is not posed. Cystic hygromas, like cervical teratomas, are seen in infants. Cystic hygromas, however, are considered developmental defects of the lymphatic system rather than true tumors. The possibility of mediastinal extension should be investigated in both: cystic hygroma occasionally, and cervical teratoma more rarely (Salas et al.; Silberman and Mendelson), may grow into the upper mediastinum.

More common than cystic hygroma is the occurrence of imperfect obliteration of the embryonic branchial clefts between the branchial arches of the embryo, which may give rise to lesions that must be distinguished from cervical teratoma. Preauricular subcutaneous cysts that do not connect internally with the eustachian tube or the external auditory canal are probably of noncleft origin (Soper). Anomalies of the second branchial cleft are the most common. In infants, the most frequent form is a draining fistula or a sinus manifested as a tiny opening at the junction of the middle and lower third of the anterior edge of the sternocleidomastoid muscle. The tract extends along the carotid sheath for variable distances, up to the tonsillar fossa. At any point in this tract a cystic dilatation may develop as a result of infection and accumulation of secretions. Cystic lesions, 10 percent of which are bilateral, generally become apparent in preschoolers (Bill and Vadheim). The cysts are usually deep to the anterior border of the sterno-

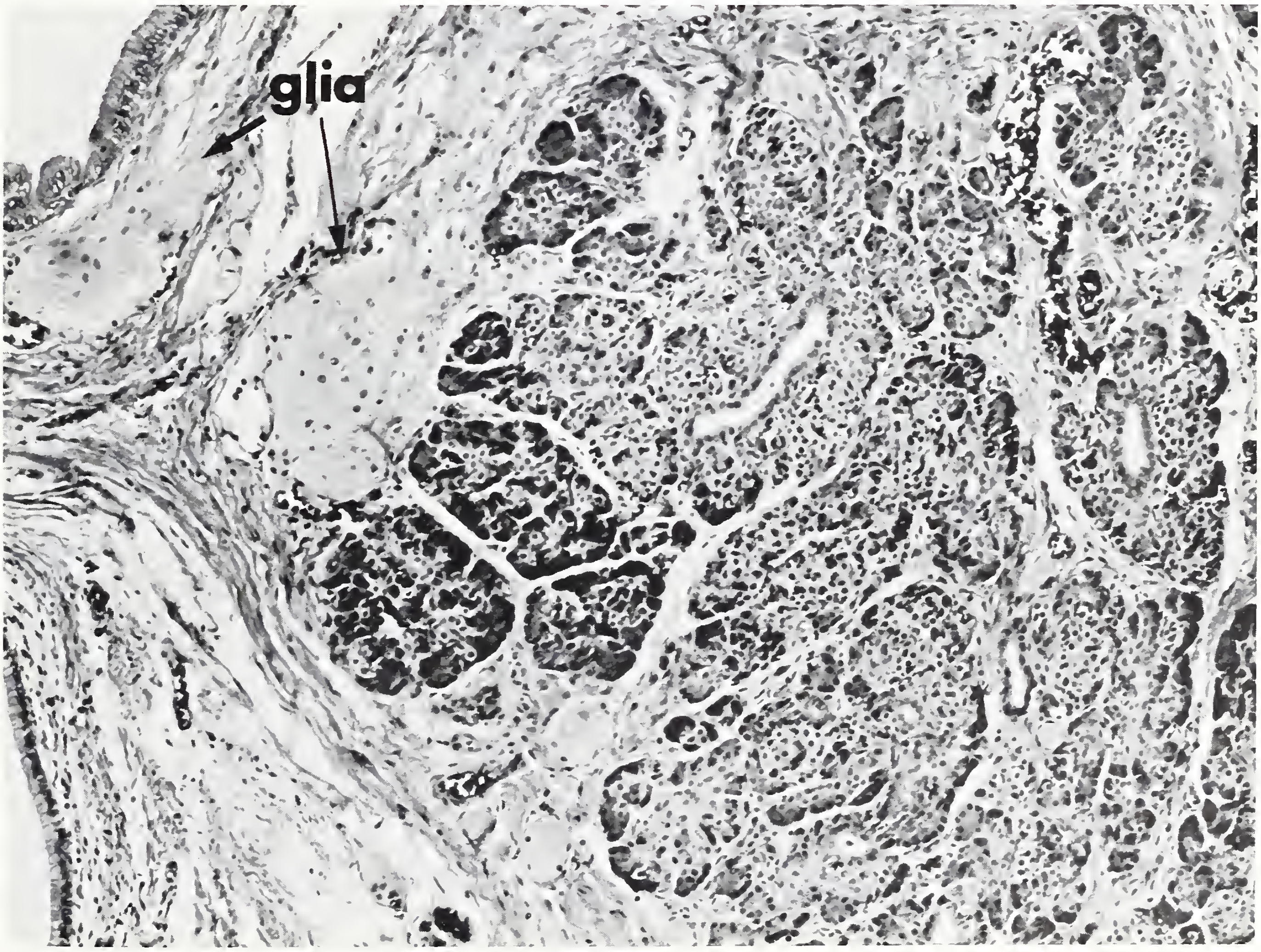

Figure 74
CERVICAL TERATOMA
Area of pancreatic acinar tissue found in neck teratoma illustrated in figure 73. X275.

cleidomastoid muscle. Anomalies of the first branchial cleft and arch are less common. The cysts are then located in front of the ear, or in submandibular location, whence they may extend to the external auditory canal (Lincoln). As with those originating in the second branchial cleft, sinuses and fistulae of the first arch and cleft may give rise to cysts. The age at which these cystic lesions present is of importance in the distinction from cervical teratoma. Histologically, the cyst lining consists of squamous epithelium in 90 percent of the cases (Soper); respiratory epithelium and lymphoid tissue may also be found.

Thyroglossal cysts arise from remnants of the thyroglossal duct, anywhere between the base of the tongue and the midpoint of the hyoid bone on a median, or very close to median, location. The midline position of these lesions is their outstanding clinical characteristic, and one that permits the correct diagnosis in most cases. These lesions are also seen most frequently in the preschool years. Therapy aims at complete removal of all the duct remnants, and this usually means removal of the central part of the hyoid bone.

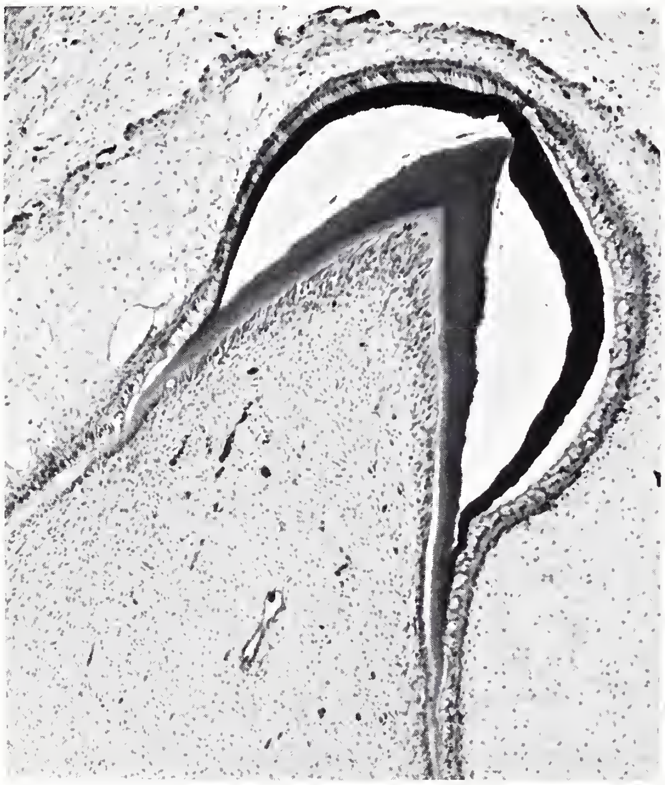

Figure 75
CERVICAL TERATOMA
Tooth germ present in neck teratoma with advanced differentiation. X25.

Roediger and associates drew a distinction between true teratomas and "complex cysts" of the thyroid. The former show multiorganoid differentiation, whereas the latter, in their opinion, represent hamartomas. These lesions are composed of respiratory and squamous mucosa, and may show cartilage in their walls, either because of origin from the larynx, or due to metaplasia of thyroid parenchyma. Lesions of seemingly similar nature are sometimes reported as "choristomas" of the neck. Tang and associates described a lesion arising in the submandibular salivary gland of a neonate, not related to the thyroid. Microscopically, it was composed of numerous cysts lined by various epithelia and often surrounded by smooth muscle. Because only endodermal derivatives were present, this lesion was interpreted as a choristoma rather than a teratoma.

Uncommonly, the root of the neck may be the site of cysts that more properly belong in the mediastinum. These include bronchogenic or thymic cysts that may have been displaced from the upper mediastinal compartment into the base of the neck (Soper).

Infrequently, the preoperative distinction should be established between congenital goiter and cervical teratoma. In the past, congenital goiter was seen in endemic areas (Saphir). Today, goiter in the newborn infant may be due to ingestion of goitrogens by the mother during pregnancy, or to inherited enzymatic defects in

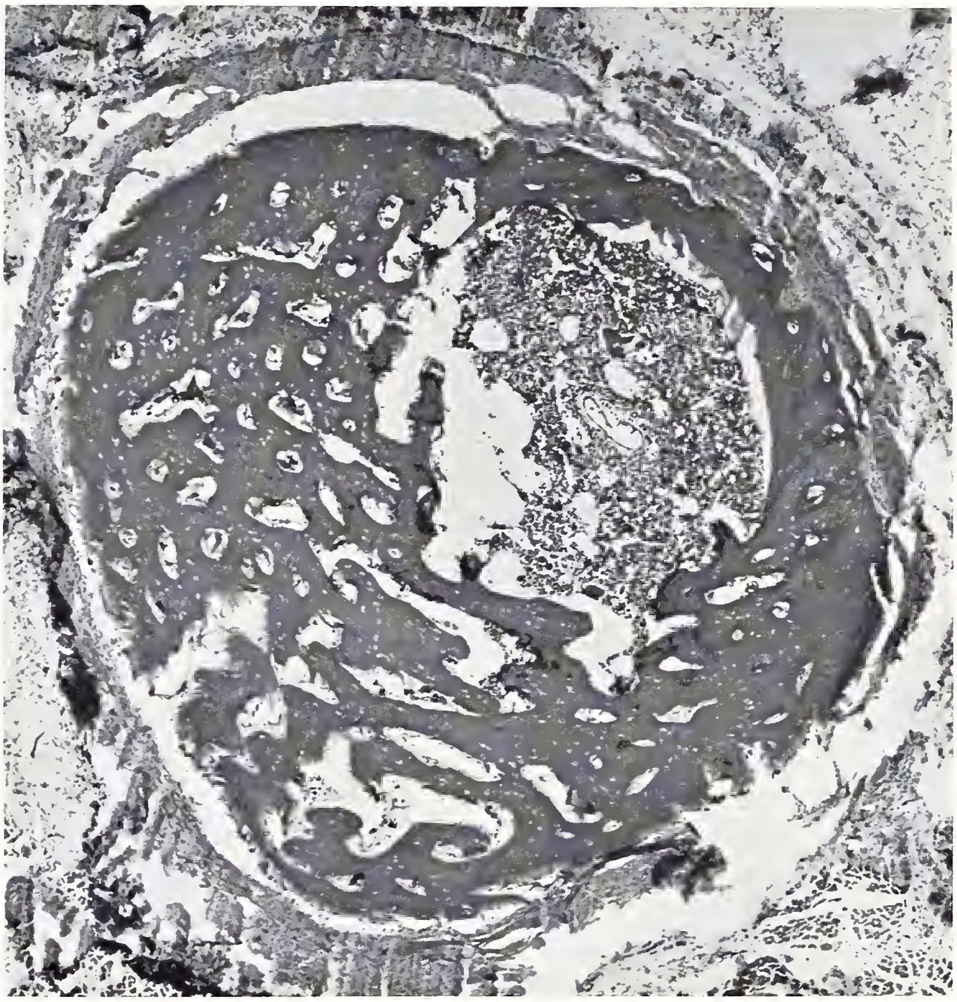

Figure 76
CERVICAL TERATOMA
Well organized bone in anterior cervical teratoma with pronounced organoid differentiation. X25.

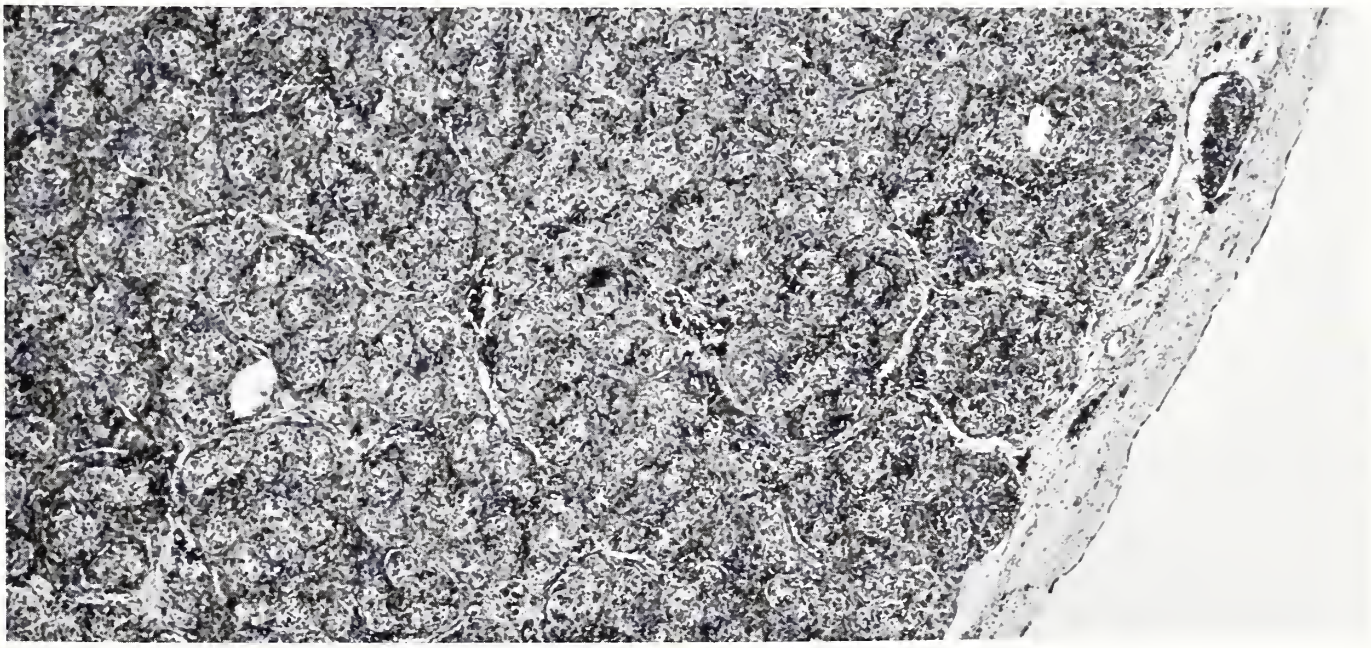

Figure 77
CERVICAL TERATOMA
Nodule shown in plate IV-A corresponds to fully differentiated male gonad. The absence of gonadal tissue in most teratomas raises the suspicion of a parasitic twin. X25.

the synthesis of thyroid hormones. When the teratoma occupies the area of the thyroid gland and reproduces the shape of the gland, the distinction may not be apparent until operation, but the presence of calcifications may be helpful to establish the diagnosis. In adults, the possibility of a primary thyroid carcinoma should be ruled out.

Prognosis. Malignancy has been said to occur in approximately 5 percent of teratomas of the neck (McGoon). Since teratomas of this anatomic area are uncommon, the presence of a malignant tumor arising in a cervical teratoma must be considered exceptional. We know of no case of documented malignancy during childhood. However, a large proportion of patients with cervical teratoma (more than 25 percent of those reviewed by Silberman and Mendelson) died prior to surgery. Hence, unless surgery is instituted without delay, the prognosis of cervical teratoma can be serious. This grave outlook seems to depend largely upon obstruction of upper respiratory passages. Tracheostomy may be very difficult without removal of the tumor in patients presenting with very large masses. Often, these are so situated as to preclude access to the trachea. With less than complete larynogotracheal occlusion, the degree of interference with deglutition may be severe. In prenatal life this causes polyhydramnios (Rosenfeld et al.); postnatally, it may lead to aspiration of secretions, atelectasis, and bronchopneumonia.

Treatment. The operative mortality has been reported at between 9 percent (Silberman and Mendelson) and 17 percent (Hajdu et al.; Hurlbut et al.). Removal of the tumor is the treatment of choice for this condition. There is no evidence that radiation is beneficial, and it carries potential risks.

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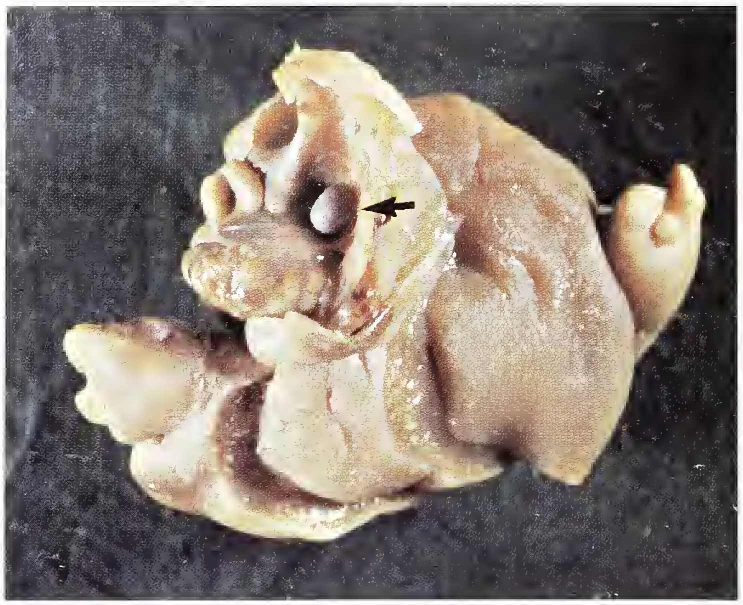
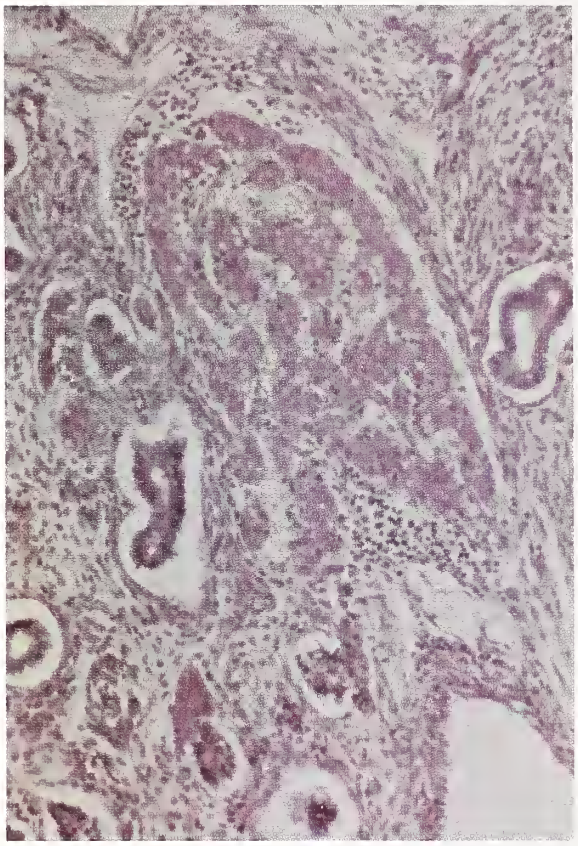
PLATE IV



A. CERVICAL TERATOMA

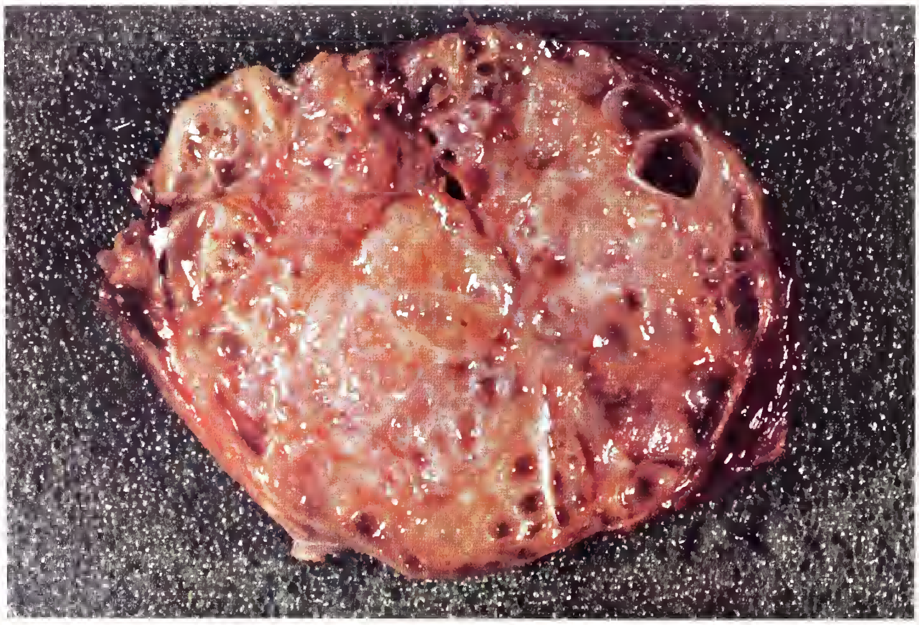
(Plate IV-A and figures 73-77 from same case)

Highly differentiated organotypic development of an anterior neck mass of a male newborn infant. Because of the formation of complex tissue structures, including a well developed male gonad (arrow), these lesions are difficult to distinguish from a conjoined twin. The thryoid was replaced by the mass.



B. HEPATIC TERATOMA

Microscopic features of hepatic morphogenesis in a benign teratoma of liver, with high levels of alpha fetoprotein in the serum. Original magnification X50. (Courtesy of Dr. Takuji Todani, Okayama, Japan.)



C. GASTRIC TERATOMA

Cut surface of a congenital gastric teratoma with cystic and solid components.

TERATOMAS OF THE LIVER

True teratomas occur within the liver very uncommonly. According to Todani and associates, 24 cases had been reported up to 1977, of which 17 were in children and 7 in adults. A predominance of females has been observed, but the number of cases is too small for adequate statistical assessment. Only 1 of 41 consecutive patients with primary liver neoplasms treated at the Columbus Children's Hospital between 1950 and 1974 had a teratoma (Misugi and Reiner). Similarly, only 1 of 22 primary tumors of the liver recorded at the Children's Memorial Hospital of Chicago between 1954 and 1979 was a teratoma (Nikaidoh et al.). The etiology has remained unknown. Genetic imbalance may be related to the origin of some hepatic teratomas. Dische and Gardner described a male fetus with 13 trisomy in which the rare association of teratomas of the neck and liver was present, together with the expected multiple anomalies.

Clinical Features. Most patients receive medical attention because of the presence of an abdominal mass. The tumor is apt to manifest itself before the patient is 3 years old as an abdominal protuberance, or a mass palpated by the patient's parents or custodians. There may be weight loss, vomiting, irritability, or abdominal pain, but all these manifestations have been less prominent and less useful diagnostically than the presence of an abdominal mass. The mass is most commonly found in the right upper abdominal quadrant or epigastrium, and generally moves with respiratory movements.

Laboratory and Roentgenologic Examination. Clatworthy and associates deemed most laboratory studies of limited value in the preoperative evaluation of a child with a primary liver tumor. Alkaline phosphatase was rarely elevated in these cases, and, except for the presence of jaundice and occasional cirrhosis, liver function tests tended to be within normal limits. The value of serum alpha-fetoprotein levels in the diagnosis of hepatoblastoma is now well established, but, as discussed later, this abnormal serum protein was found in a patient with a benign hepatic teratoma.

Conventional roentgenographic (fig. 78) and scanning technics are currently con-

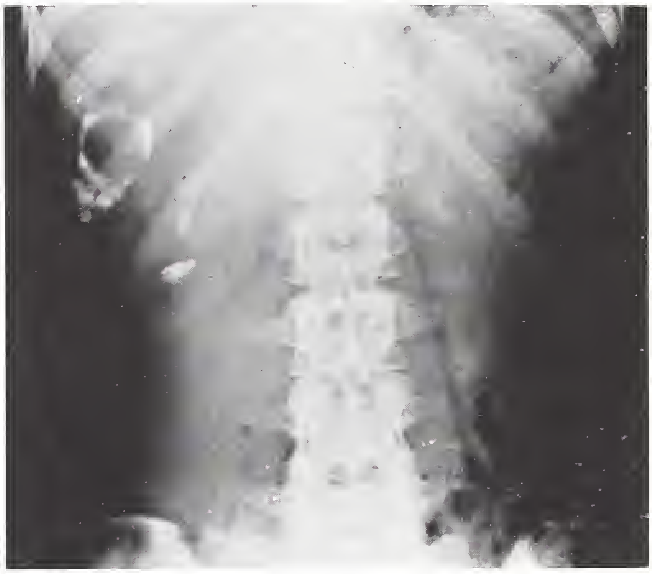


Figure 78
(Figures 78, 79, and 81 from same case)
HEPATIC TERATOMA
Plain film of the abdomen reveals characteristic organized calcification surrounding the entire periphery of a cyst in a hepatic teratoma. Note adjacent densities suggestive of teeth crowns. (Courtesy of Dr. I. Watanabe, Sendai, Japan. From Watanabe, I., Kasai, M., and Suzuki, S. True teratoma of the liver — report of a case and review of the literature. Acta Hepatogastroenterol. [Stuttg.] 25:40-44, 1978.)

sidered indispensable for adequate preoperative localization of liver tumors. Chest x-ray films and bone surveys should be routinely obtained to check for metastatic tumor spread. Intravenous pyelogram and inferior cavogram may reveal distortions of the normal anatomic relationships. Liver scans assist not only in the establishment of the diagnosis, but also in the preoperative assessment of its extent. Teratomas tend to appear as "cold" spots on the scan. Of particular interest in the delineation of operability is serial hepatic arteriography, which can provide accurate information on the vascular anatomy of the tumor.

Gross Appearance. Benign hepatic teratomas have appeared as well encapsulated masses that may acquire voluminous dimensions (Imai; Kasai and Watanabe; Leschke; Minor; Misick; Misugi and Reiner) and replace the liver parenchyma. The tumor tissue is grossly identical to teratomas of other sites, namely, composed of alternating cystic and solid areas. One of the few authenticated malignant teratomas of the liver appeared grossly noncystic (Misugi and Reiner), whereas benign tumors have been grossly cystic (figs. 79, 80).

Microscopic Appearance. A wide diversity of tissues is present, which represents derivatives of the three germ layers. Todani and co-workers estimated that of the published cases, 90 percent of hepatic teratomas contained liver cells as an integral part of the tumor. Among unusual tissue components present in hepatic teratomas have been pancreas (Froboese; Pear and Boline; Yarbrough and Evashwick), urinary tract tissues (Misugi and Reiner; Pear and Boline), and endocrine tissue (pl. IV-B; figs. 81, 82). Gonadal and ocular tissues were observed in a hepatic teratoma of a 32 year old man (Clatworthy et al.). The presence of liver tissue in teratomas has been considered unusual; Gaillard is of the opinion that it occurs more frequently than is suspected, but that it often goes unrecognized because of the primitive appearance that it tends to adopt when present. He illustrated cords of primitive-looking hepatic parenchyma in testicular endodermal sinus tumors, which he considers to be "simplified teratomas." A tumor of endodermal sinus pattern has been described that apparently was primary in the liver (Hart). The patient, a male child, died and was not

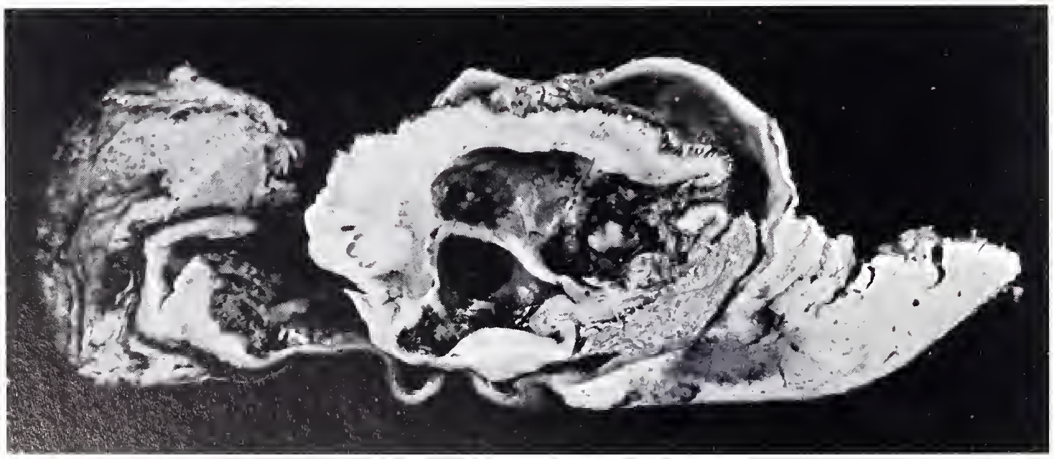


Figure 79
HEPATIC TERATOMA
Cut surface of fixed specimen shows the apparent encapsulation and cystic nature of the tumor. (Courtesy of Dr. I. Watanabe, Sendai, Japan.)

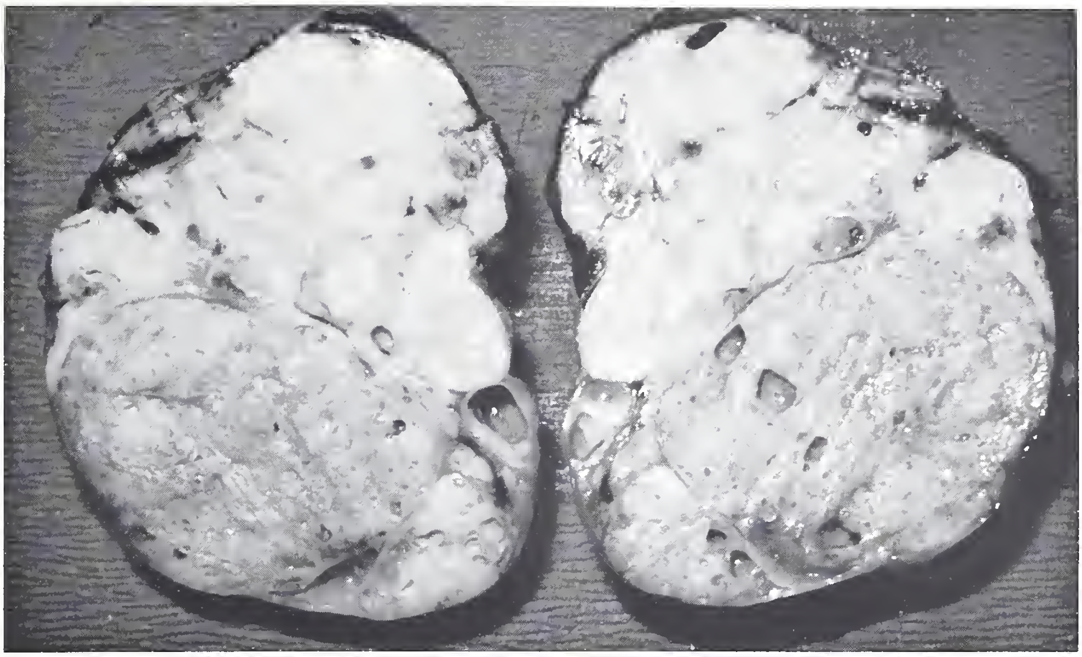


Figure 80
HEPATIC TERATOMA
Gross appearance of benign teratoma of the liver. Although grossly reminiscent of hepatoma, a distinct cystic component may be seen. (Courtesy of Dr. Takuji Todani, Okayama, Japan.)

autopsied; hence, the possibility of a minute gonadal primary tumor could not be ruled out. Conversely, a teratoma of the liver was described by Watanabe and associates in a 20 year old female, eight years after treatment for dysgerminoma of the left ovary. The possibility of a metastatic focus in the liver subsequently undergoing differentiation cannot be ruled out. Squamous cell carcinoma (Kasai and Watanabe) and hepatoblastoma (Misugi and Reiner) have been described as malignant neoplastic tissues within liver teratomas.

Differential Diagnosis. A serious problem of the preoperative differential diagnosis of hepatic masses in children is that very few clinical features or radiographic findings are helpful in determining the specific nature of the problematic growth. Definitive diagnosis ordinarily requires histopathologic examination of the excised mass, and it is acknowledged that all symptomatic hepatic masses should be removed, even if this means performing a lobectomy. Furthermore, symptomatic liver masses are more often malignant than benign (Clatworthy et al.; Clatworthy and Boles). Thus, a particularly onerous decision refers to liver masses that, because of anatomic location, are dangerous to remove (Raffucci and Ramirez-Schon).

Histopathologically, the differential diagnosis must include primary liver cell tumors, i.e., hepatocarcinoma and hepatoblastoma. In general, the relatively homogeneous histologic composition of these neoplasms will permit their correct identification. A liver cell origin is usually apparent in most hepatocarcinomas, tumors which only rarely occur in patients below the age of 6 years. Hepatoblastoma of children is also identifiable as a tumor originating from hepatocytes. A "pure epithelial type" is recognized, composed of fetal and embryonal liver cells (Gonzalez-Crussi and Manz). Hepatoblastomas may also be of "mixed," epithelial, and mesenchymal histologic composition (Hartz and

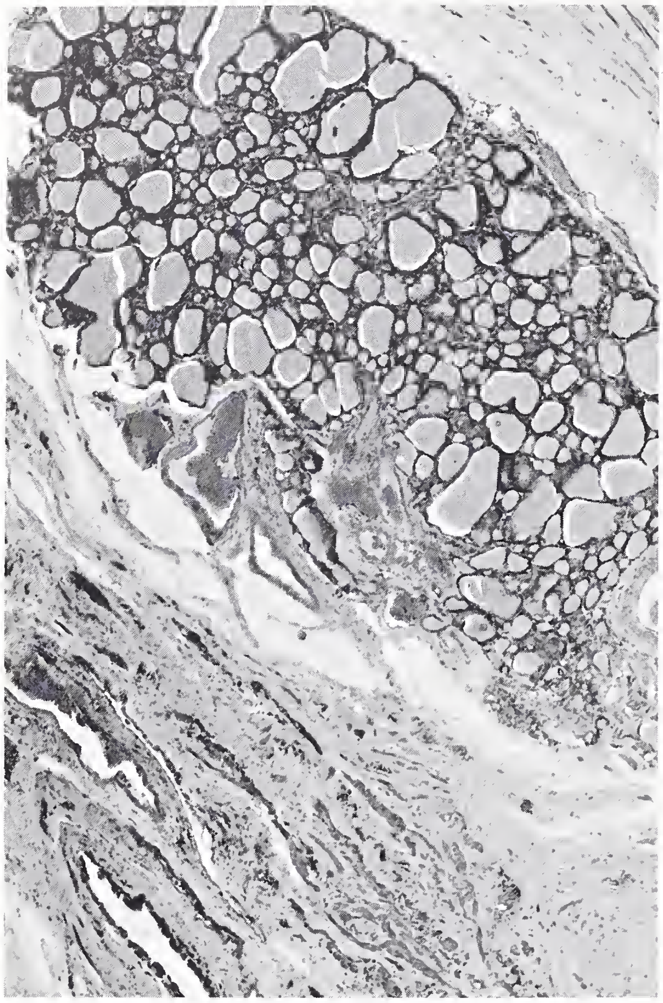


Figure 81
HEPATIC TERATOMA
Among the tissues found in the hepatic teratoma are thyroid tissue and mesenchymal components. X60. (Courtesy of Dr. I. Watanabe, Sendai, Japan.)

van der Sar). In this case, the tumors may contain a variable proportion of mesenchymal tissues, including areas of rhabdomyosarcoma, chondrosarcoma, or fibrosarcoma. Dehner has stated that osteoid-producing tissue is the most common type of differentiated mesenchyme, present in 20-35 percent of all hepatoblastomas. The resulting microscopic appearances may be sufficiently variegated to suggest a diagnosis of teratoma. The defining feature of hepatoblastoma is a background of immature hepatocytes, whereas that of teratomas is a heterogeneity of tissue structures in which derivatives of the three germ layers are apt to be found, often with marked organoid differentiation. These criteria will ensure appropriate classification of most cases, but Dehner is correct in pointing out that in some instances the distinction between teratoma and mixed hepatoblastoma may be subtle, particularly when uncommon forms of tissue differentiation, such as melanin-containing cells and endodermal derivatives, are encountered in tumors otherwise classified as hepatoblastomas. When the full differentiative capacity of the teratoma cells is expressed, as in benign mature teratomas, the resulting appearances are diagnostic. It should not be surprising that the immature, or embryonic, tissues result in microscopic patterns of difficult characterization.

Todani and associates observed that a benign teratoma was associated with high serum levels of alpha-fetoprotein, as would be expected of hepatoblastoma. This may add to the difficulties in the preoperative differential diagnosis. Although the latter authors stated that neither yolk sac tumor nor hepatoblastoma components were present in their case, they illustrated foci of small hepatic cells within the teratoma; such well differentiated liver cells, almost indistinguishable from normal fetal or infantile liver, are known constituents of hepatoblastoma (Gonzalez-Crussi and Manz) and these could be the source of alpha-fetoprotein (pl. IV-B).

Mixed tumors arise within the infantile liver that are termed hamartomas, adenomas, and focal nodular hyperplasia (Edmondson; Rhodes et al.). Despite the composite microscopic appearance of these lesions, a problem of differential diagnosis with true teratomas is rarely posed. Teratomas and hamartomas are both congenital; however, by definition hamartomas contain cells and tissues that are found normally as

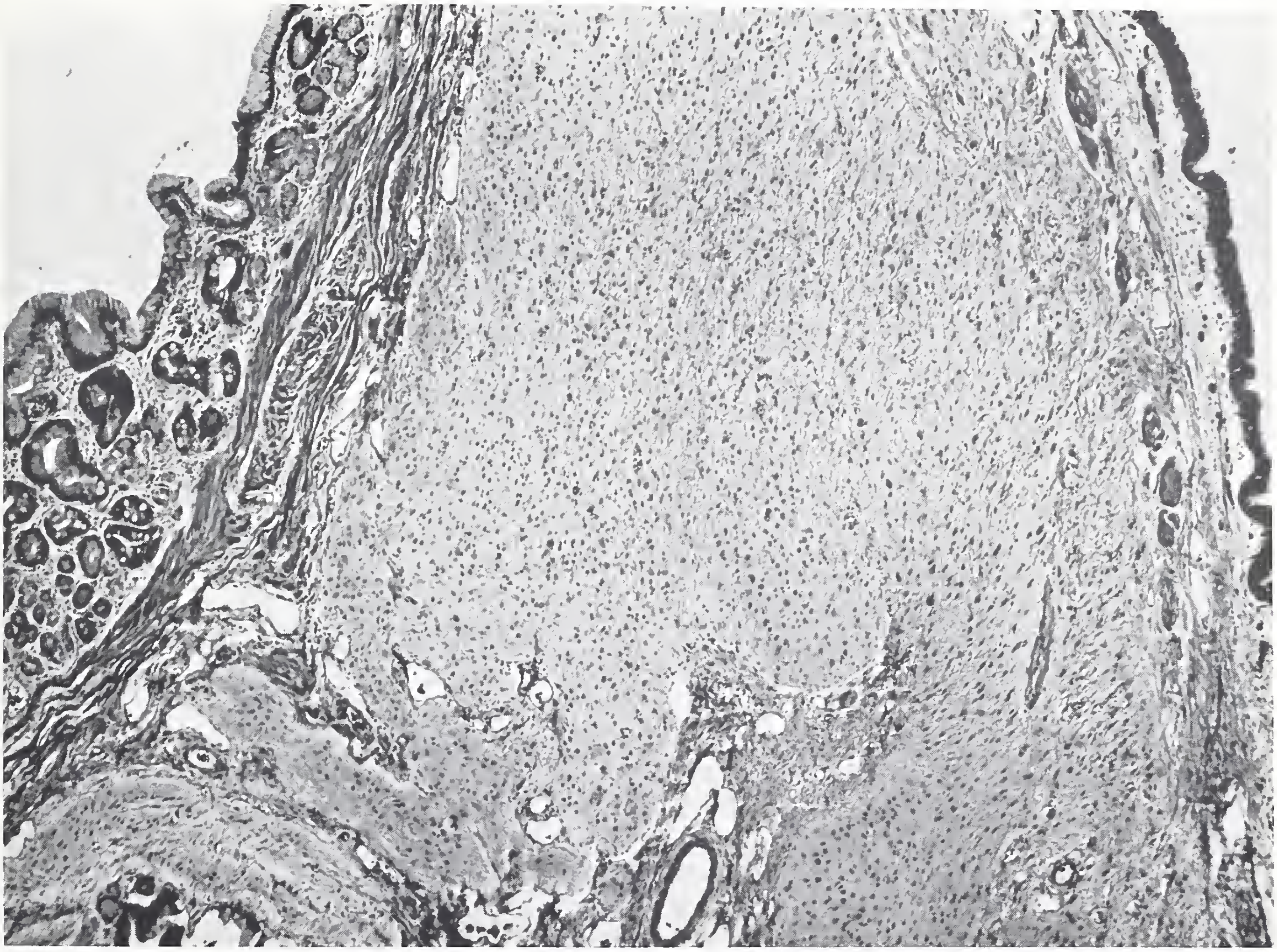


Figure 82
HEPATIC TERATOMA
Organoid development of a teratoma of the liver reproduces gastric components (left), glia (center), and ciliated epithelium (right). X120.

a part of the organ in which they arise, in abnormal arrangement, and without proclivity to progressive growth. Rhodes and associates have discussed the differential histopathologic diagnosis of different variants of primary liver hamartomas.

Prognosis. With a well differentiated teratoma, and in the absence of complications, the prognosis should be good. Survival of a 6 week old infant, operated upon under very precarious conditions, was reported at 14 years of follow-up (Yarborough and Evashwick). Dische and Gardner tabulated the clinical and pathologic findings in 15 patients with teratoma of the liver reported in the literature, including their own. In 5 of these, the operation was successful, and the patients were free of disease between 1½ and 14 years postoperatively. Three patients died without undergoing operation. No information was available in 2 others, and another was a fetus obtained by induced abortion. Two deaths were attributable to surgical complications, and 1 to recurrent tumor.

Treatment. The first successful right hepatectomy for a primary liver malignancy of childhood was performed in 1952

(Clatworthy and Boles). Since then, improved technics have enabled surgeons to attempt resection of practically all the benign liver growths and many of the malignant tumors, aiming for cure. Sharply localized tumors in patients without evidence of metastases may be treated by liberal wedge resection. With larger masses, a lobectomy becomes necessary, and with even larger tumors or those critically situated, resection may be accomplished after irradiation, with or without chemotherapy, has reduced the size of the mass. Evaluation of results of surgical treatment is difficult because of the paucity of cases and the lack of agreement on histopathologic criteria of malignancy. Moreover, disturbed pathophysiology secondary to compression or destruction of critical structures worsens the prognosis of tumors that, judged by histology alone, would have been deemed benign (Kasai and Watanabe).

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TERATOMAS OF THE STOMACH

Teratomas originating in the stomach are distinctly rare. Periodically, isolated cases are reported and the literature is reviewed. Thus, in 1969, De Angelis found 16 previously published cases and added 1 more. In subsequent reviews (Aubrespy and Derlon; Azpiroz et al.; Bandi et al.; Moriuchi et al.; Ogami et al.), the number of cases increased gradually, and by 1975 Morrison and co-workers could find 39 instances. A few have been added since, but less than 50 well documented examples exist in the literature.

It used to be customary among reviewers to state that all gastric teratomas occur in male infants. The documentation of a gastric teratoma in an elderly female (Prieto Sánchez et al.) makes it necessary to revise this statement. Nonetheless, the overwhelming predominance of patients of male sex is indisputable; there are apparently only rare exceptions to the rule of male involvement in gastric teratoma (Moriuchi et al.). This distinct sex preference is especially intriguing in view of the predominance of females with teratomas of the most prevalent anatomic types, gonadal and sacrococcygeal. No cogent hypothesis has been advanced to account for this distribution. There has been no mention of associated conditions or congenital anomalies in patients with gastric teratoma. The presence of hiatal hernia (Cooray and Jayartne) or reflux esophagitis (Atwell et al.) possibly depends on local conditions resulting from the development of a large gastric mass, or from the effects of surgery.

Clinical Features. Gastric teratomas can be large enough to cause diaphragmatic elevation and respiratory difficulty in the newborn period (Cooray and Jayartne), but an accurate clinical diagnosis is extremely difficult. The nature of the growth has been established in virtually all cases only after operation and histopathologic examination. When the tumor is not palpable the diagnosis may be delayed, but in the majority of cases the symptoms have required investigation and treatment before the patient reaches 1 year of age. Next to the presence of a palpable mass, the patients with gastric teratoma have had the following manifestations, in order of decreasing frequency (Morrison et al): abdominal distention, vomiting, hematemesis or melena, respiratory distress, anemia, fever, weakness, abdominal pain, feeding problems, and constipation.

Roentgenologic and Laboratory Examination. Usually these tumors produce ill-defined shadows that fill a large part of the left upper abdominal quadrant (fig. 83). Approximately half the tumors had roentgenologic evidence of intratumoral calcifications (fig. 84); in two patients these took the form of well organized bone or teeth (Morrison et al.). Calcification tends to be in large deposits, whereas in Wilms' tumor it is rare, and in neuroblastoma it often appears as "flecks." A gastrointestinal series reveals the filling defect representing a gastric mass (fig. 85). With very large gastric masses there may be displacement of the bowel to the right and caudally. Intravenous pyelography, especially useful to distinguish a primary renal tumor, tends to be normal in gastric teratoma. Retrograde aortography and ultrasonic ecogram

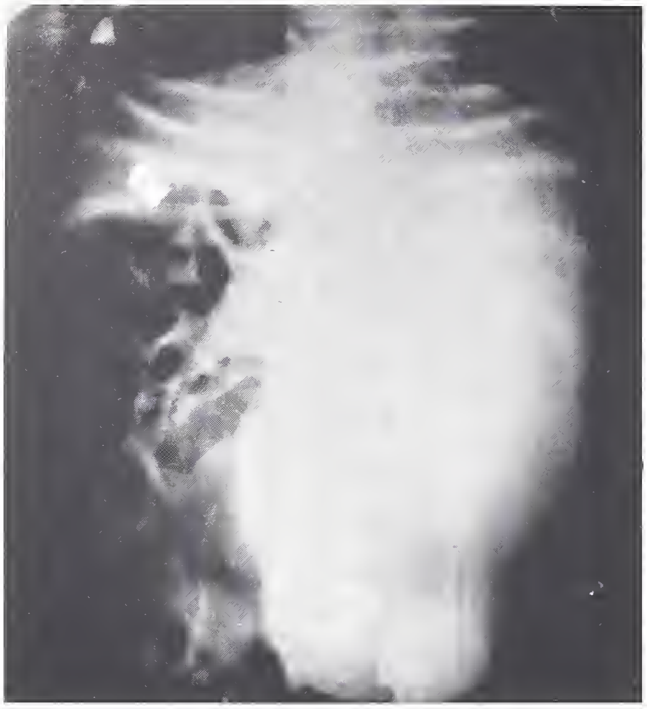

Figure 83
(Figures 83, 86, and 87 from same case)
GASTRIC TERATOMA
Homogeneous opacification of a large part of the abdomen, produced by a large teratoma of the stomach in a newborn infant. (Courtesy of Dr. Carlos Sariñana, Mexico City, Mexico.)

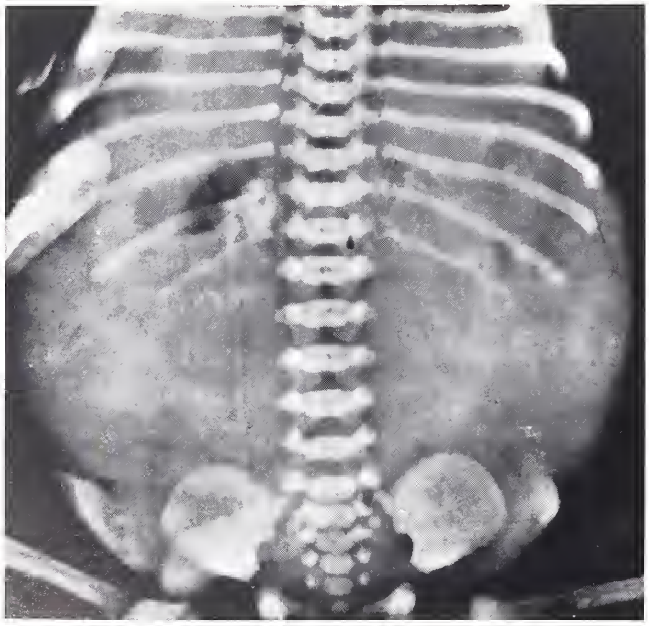

Figure 84
(Figures 84 and 85 from same case)
GASTRIC TERATOMA
Plain film of the abdomen of a newborn male infant shows virtual absence of gas and the presence of a centrally placed calcified mass. (From Siegel, M. J. and Shackelford, G. D. Gastric teratomas in infants: report of two cases. Pediatr. Radiol. 7:197-200, 1978.)

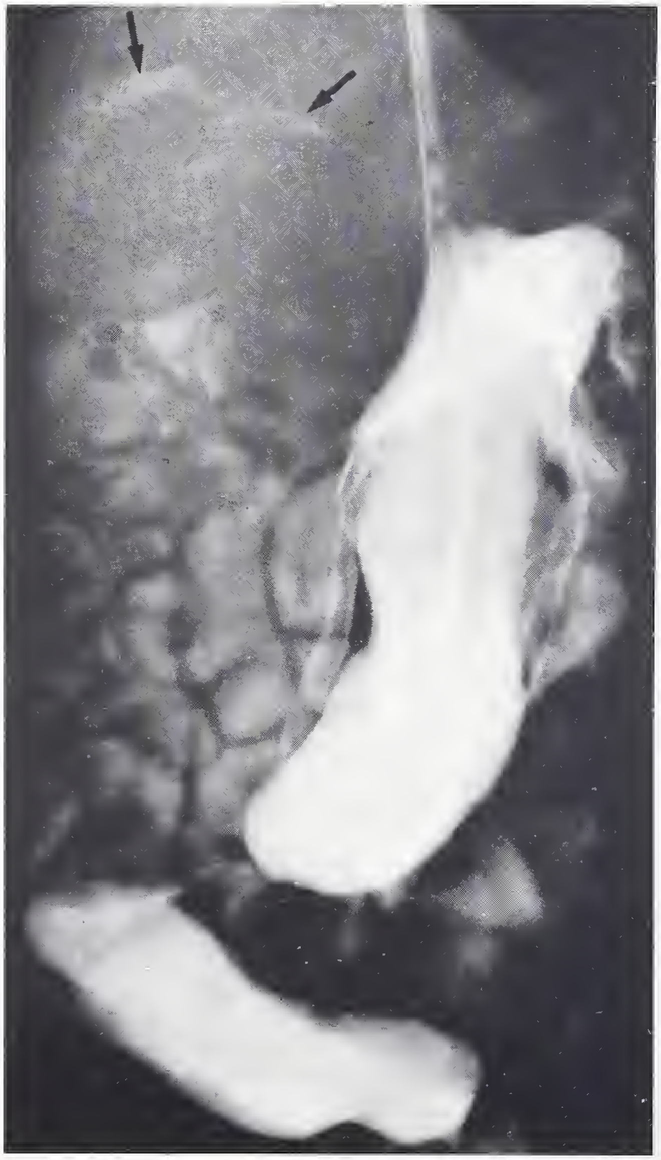

Figure 85
GASTRIC TERATOMA
Lateral film from upper gastrointestinal series shows a calcified soft tissue mass (arrows) displacing the stomach inferiorly and posteriorly. (From Siegel, M. J. and Shackelford, G. D. Gastric teratomas in infants: report of two cases. Pediatr. Radiol. 7:197-200, 1978.)

may also be useful to distinguish gastric teratomas from other intra-abdominal neoplasms. Ultrasonography usually shows cystic and solid components in the tumor (Siegel and Shackelford). Search for catecholamine metabolites in the urine should be of help to distinguish neuroblastoma from other intra-abdominal tumors in infants.

Gross Appearance. The largest tumors have reached measurements of 20 cm. and weighed over 1000 g. (Moriuchi et al.; Sariñana et al.; Selman). Growth may be predominantly intragastric or extragastric. Since the mass usually cannot be dissected free from the stomach, a greater or lesser segment of this organ must be removed together with the tumor (pl. IV-C; figs. 86, 87). Some tumors have shown a combined endogastric and extragastric manner of growth. Any part of the stomach may be involved, from the cardia (Giacomoni and Zaffaroni) to the pylorus, but the most frequent have been the posterior wall and lesser curvature (Atwell et al.; Aubrespy and Derlon; Azpiroz et al.; Bandi et al.). Teratomas of the stomach in infants tend to be proportionately very large, thus accounting for their early detection, although the largest one has been in an adult (Morrison et al.).

Microscopic Appearance. The microscopic appearance is that of benign teratomas. Multiple epithelial-lined cysts, islands of glial tissue resembling brain, skin appendages, and cartilage are the tissues most often seen. Whereas for the most part these tissues appear fully differentiated and mature, the existence of immature neural tubular structures and other immature somatic tissues is documented in gastric teratomas (Moriuchi et al.). No distinctly malignant germ cell elements have been observed thus far in these tumors (figs. 88–91) when discovered in infants. It

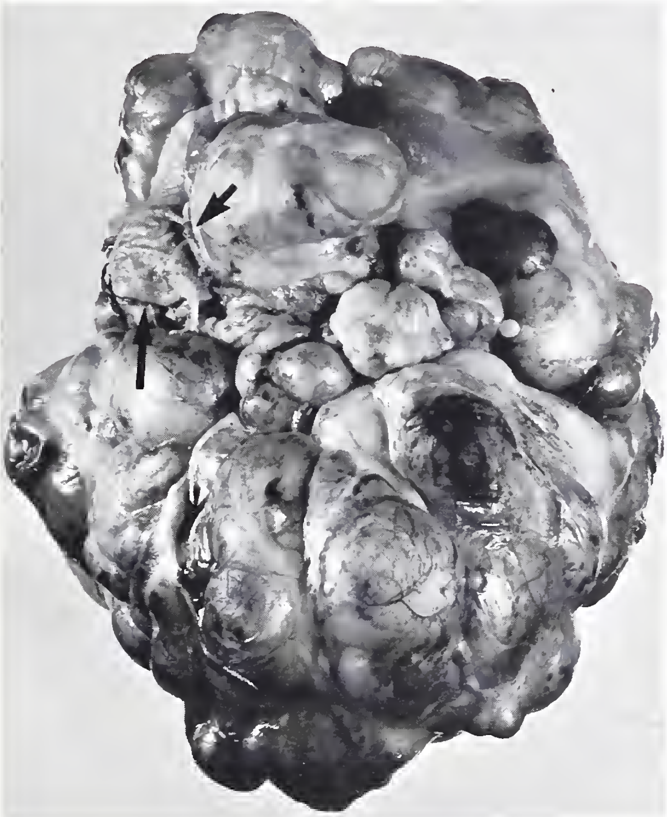

Figure 86
GASTRIC TERATOMA
Operative specimen with fluctuant, external surface. Arrows point to the segment of gastric wall that was unavoidably removed together with the tumor. (Courtesy of Dr. Carlos Sariñana. Mexico City, Mexico.)

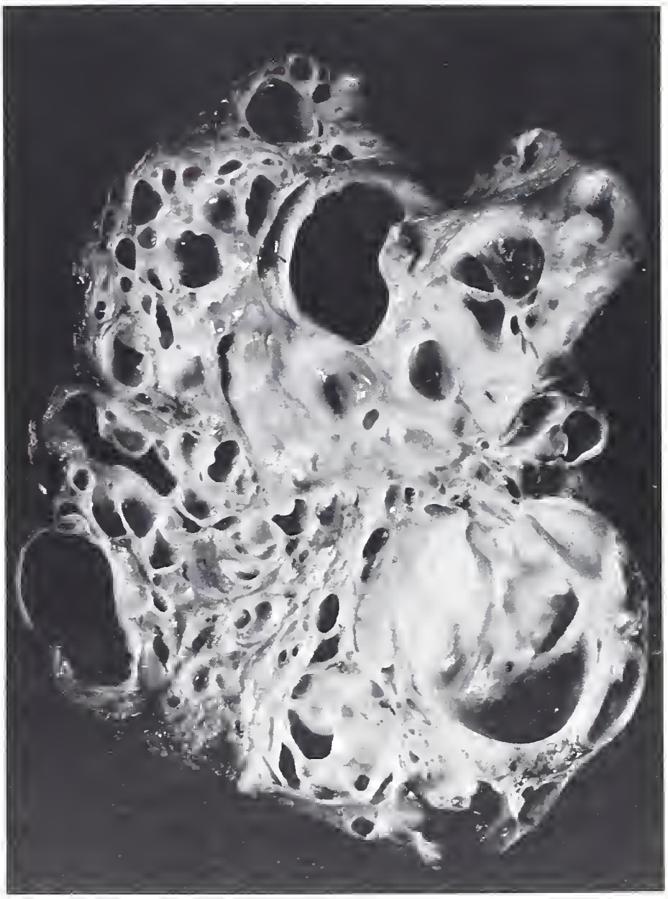

Figure 87
GASTRIC TERATOMA
Cut surface of specimen illustrated in the preceding figure shows the multicystic nature of the teratoma. (Courtesy of Dr. Carlos Sariñana. Mexico City, Mexico.)

should be noted, however, that "pure" choriocarcinoma of gastric localization was well documented by Regan and Cremin, who were able to collect 16 previously published cases. A yolk sac tumor probably originating in the stomach is also on record (Møller and Raahave). These tumors have arisen in young adult individuals, predominantly of male sex, and their histology has been the same as that of their gonadal counterparts. If one endorses the germ cell hypothesis of origin of teratomas, it is not unreasonable to expect that a malignant teratoma with a germ cell tumor component might develop in the stomach. No such observation has been made thus far.

Differential Diagnosis. Since these tumors present as intra-abdominal masses, the differential diagnosis usually has included Wilms' tumor (Selman), neuroblastoma (Handelsman et al.), and congenital cysts (Paul et al.), lesions that are comparatively more common in infants. Among the uncommon malformations that may give rise to preoperative difficulties in the differential diagnosis, duplication of the stomach should be mentioned. This condition is more common in females (2:1), affects the greater curvature in most cases, and occasionally coexists with hemivertebrae (Pruksapong et al.). The large teratomas may cause displacement of neighboring viscera, thereby increasing the difficulties in interpretation of the roentgenologic studies. Handelsman and associates performed needle biopsy in one case, and this led to the erroneous diagnosis of neuroblastoma; it should be apparent that this procedure is not recommendable in teratomas, because the frequent presence of immature tissues may simulate various types of malignancy. The rarity of gastric

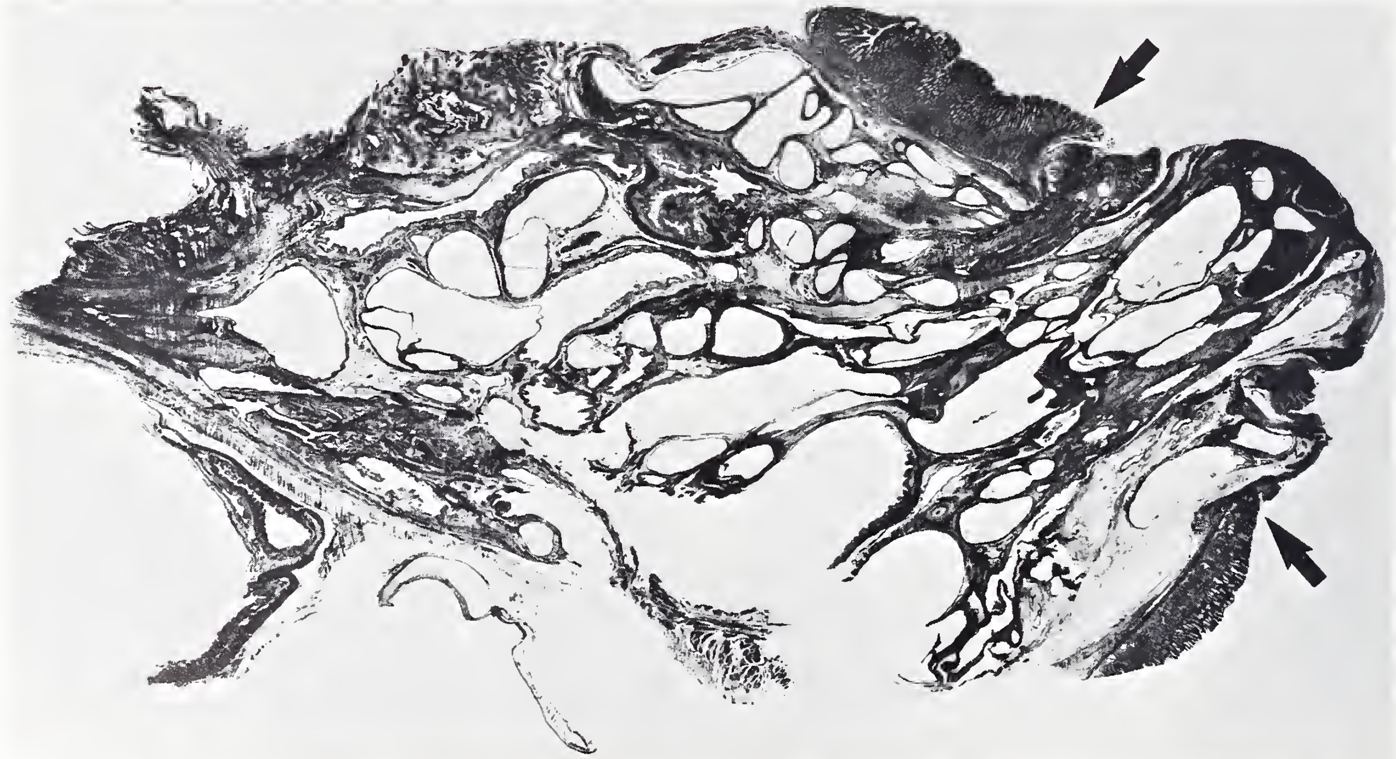

Figure 88
GASTRIC TERATOMA
Multicystic gastric teratoma largely replaces the submucosa. The mucosa of the stomach is interrupted at the points indicated by arrows, and a polypoid tumor projection passes through the ulcer. X4.5.

teratomas and the many attending diagnostic difficulties ordinarily preclude establishment of the diagnosis until the time of surgical intervention. When a teratoma is suspected, the chances of its having a retroperitoneal location far exceed the statistical probability of gastric origin (Atwell et al.). Retroperitoneal teratomas have, on occasion, perforated into adjacent structures, including the stomach (Caroli et al.).

In adult patients, gastric teratoma is even more uncommon than in infants (Gray et al.; Morrison et al.; Prieto Sánchez et al.). The most important differential diagnosis is gastric adenocarcinoma. The correct diagnosis in adult patients is usually established by frozen section of a tumor with the preoperative diagnosis of primary gastric cancer.

Prognosis. There is no documentation of invasive growth or metastatic disease in any of the reported cases of gastric teratoma. Of the 39 patients reviewed by Morrison and co-workers, 3 died. These three deaths were considered to be the result of complications, and none was attributable to the intrinsic malignant potential of the neoplasms.

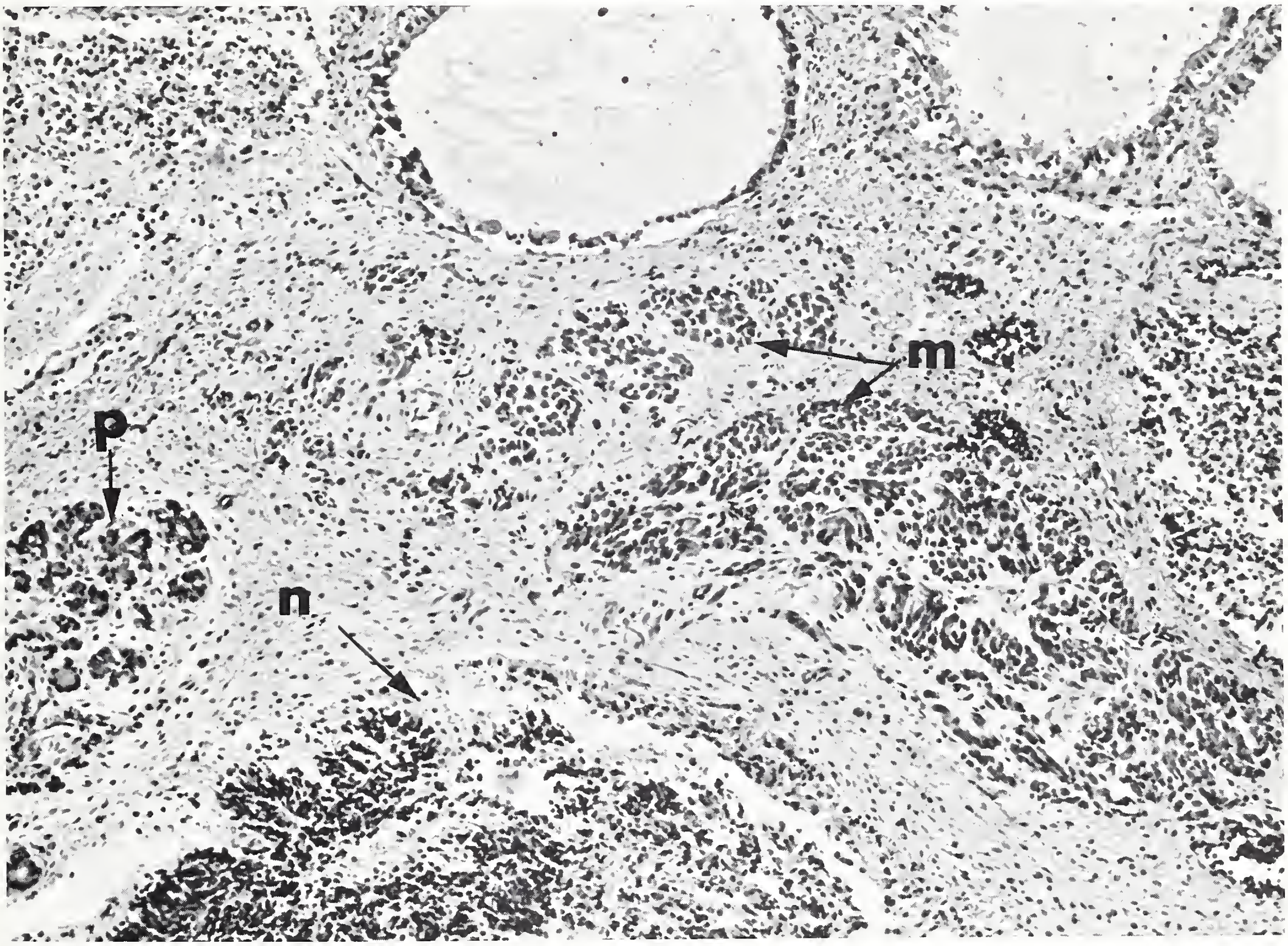

Figure 89
GASTRIC TERATOMA
Multiplicity of tissues in congenital gastric teratoma include pancreas (p), immature neural tissue (n), and striated muscle (m). Although these tissues are not mature, their histologic appearance is in keeping with the young age of the patient. No evidence of recurrence or metastases. X50.

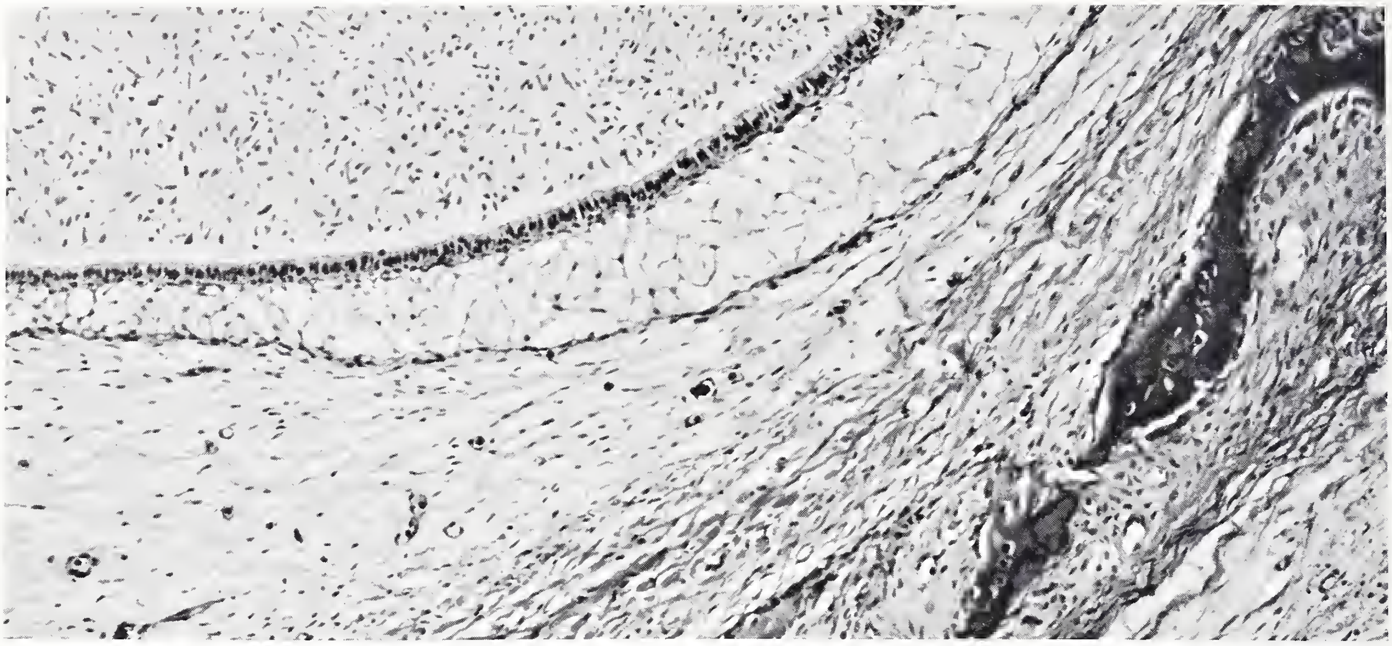

Figure 90
GASTRIC TERATOMA
Tooth germ found in gastric teratoma. Adjacent to the tooth primordium is seen an ossifying structure, possibly representing induction of bony socket. X180.

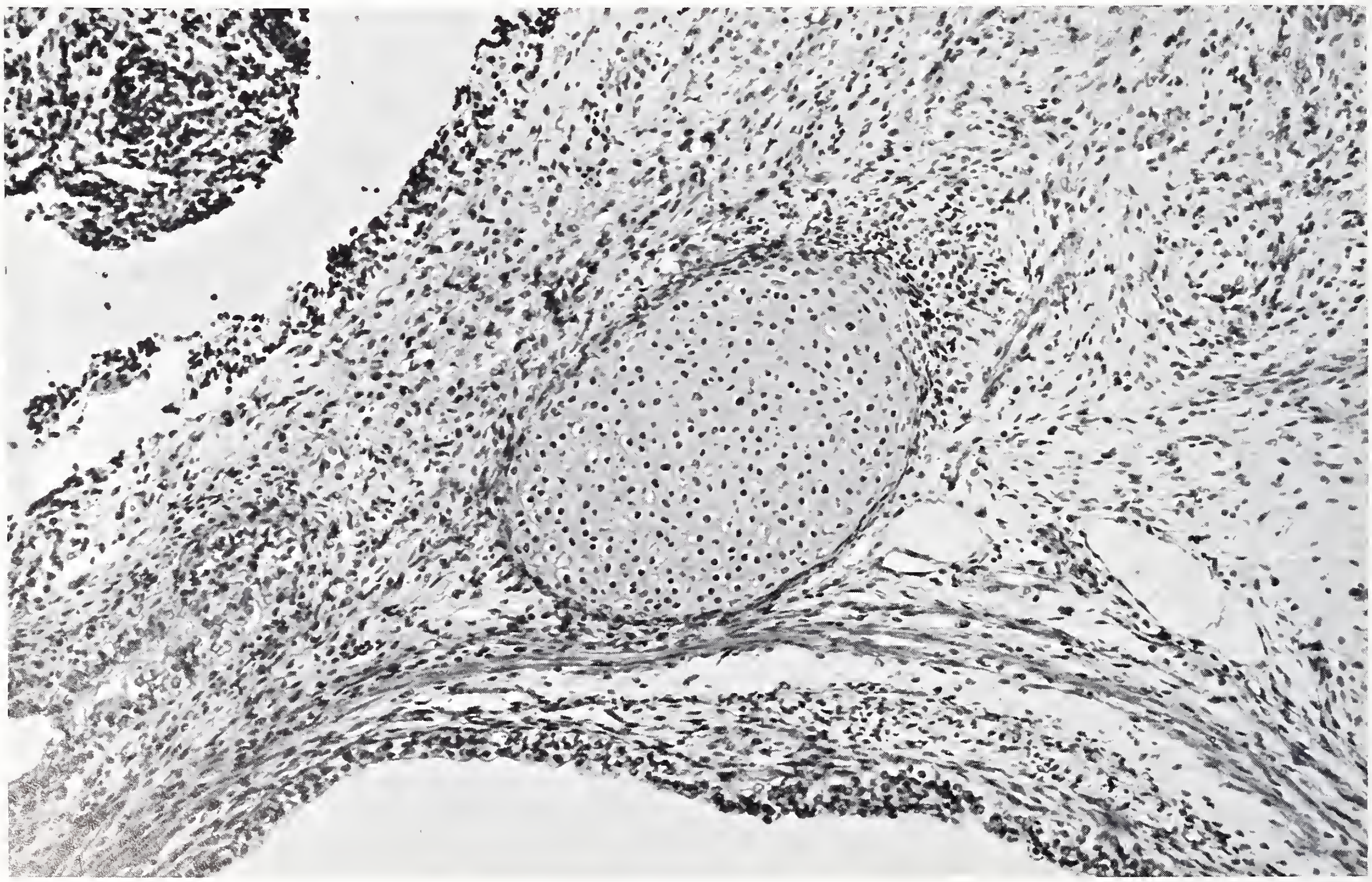

Figure 91
GASTRIC TERATOMA
Multiplicity of tissues in gastric teratoma, appearing well differentiated. X125.

Treatment. A limited subtotal gastrectomy with complete removal of the tumor offers a good chance of cure. The two patients reported by Atwell and associates were free of disease after this procedure for 5½ and 2½ years, respectively. Other reports have documented a disease-free interval of 4 years (Aubrespy and Derlon) and 13 years (Collins et al.). It thus appears that surgery should be reasonably conservative. The long-term effects of removal of a large segment of the stomach in a young child must be held in consideration. These include chronic iron deficiency anemia, megaloblastic anemia, mild protracted steatorrhea, and growth deficiency (Atwell et al; Collins et al.).

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TERATOMAS OF THE RETROPERITONEUM

SYNONYMS AND RELATED TERMS: Retroperitoneal teratoma; perirenal teratoma; pararenal teratoma; unattached retroperitoneal teratoma; extragonadal germ cell tumor; primary extragenital retroperitoneal germinoma; retroperitoneal seminoma.

In a historical review of the subject, Pantoja and associates noted that the macroscopically distinctive teratomas originating in the retroperitoneum were recognized by Morgagni and Benivieni in the second half of the eighteenth century. Early descriptions failed to establish a distinction between retroperitoneal and mesenteric lesions, since tumors in the former locations may grow anteriorly, spreading apart the mesenteric serosal sheaths, and thus appearing to originate as primary mesenteric tumors. Currently, the term retroperitoneal is reserved for those lesions that take origin from the anatomic space bounded anteriorly by the posterior sheath of the peritoneum, superiorly by the diaphragm, posteriorly by the posterior abdominal wall, and inferiorly by the brim of the pelvis, without apparent connection to the organs that reside normally in such space. The latter characteristic accounted for the term "unattached," which was formerly used in connection with these tumors (Hansmann and Budd), but which has now fallen into disuse.

Palumbo and co-workers reviewed the literature in 1949 and found 58 cases of retroperitoneal teratomas. Arnheim, in 1951, collected 39 examples appearing in infants and children. Only 29 additional cases had been added up to 1968 (Engel et al.). Pantoja and associates again reviewed the subject in 1976, and noted the infrequency of occurrence of these tumors. None of the 101 retroperitoneal tumors reported by Braasch and Mon was a teratoma. Sariñana and co-workers estimated the incidence at 1 per 9431 admissions at a major Children's Hospital in Mexico City; this figure was considerably higher than the incidence of 1 per 170,000 hospital admissions derived from other series reviewed by those authors and might indicate a certain preference of the disease for some geographic sites and ethnic groups.

Clinical Features. The patients have ranged in age between newborn infants and individuals in the sixth decade of life (Engel et al.; Palumbo et al.). Average age was 16 years in the series reported by Engel and associates. Close to half the patients are children under 10 years of age (Arnheim; Engel et al.), and 22 of the 25 children reported by Sariñana and associates were under 17 months. The second incidence peak was reported by Palumbo and associates at the third decade of life, but in more recent series it was found at the second decade (Engel et al.), perhaps reflecting increasingly more aggressive trends in diagnostic and therapeutic procedures. Palumbo and co-workers and Arnheim reported a higher incidence among females, but this was not borne out by the review of Engel and co-workers, who noted a ratio of 3:2 in favor of males.

The chief complaints are abdominal distension, abdominal pain, nausea, and vomiting. As other retroperitoneal tumors, however, these lesions may be clinically silent. Often the presenting manifestation is asymptomatic increase in abdominal girth or a mass discovered during routine physical examination. Each side of the retroperitoneum has been claimed to be preferentially involved in different series (Arnheim; Charles; Engel et al.; Palumbo et al.). In contrast with some malignant retroperitoneal tumors, there is usually no evidence of severe constitutional disturbance. Low-grade fever is noted occasionally (Palumbo et al.; Pantoja et al.). A clinical picture of sepsis is seen with less frequency nowadays, but these tumors are reported to be susceptible to infection and the development of multiple abscesses (Pantoja et al.).

Although the tumor's proximity to the kidneys and ureters may be a cause of urinary symptoms (Talbot), these are not always present. Malignant teratomas of the retroperitoneal space may provide rapidly accumulating ascites of hemorrhagic nature (Lie). Regardless of the benign or malignant nature of the tumor, it is not uncommon to see an associated distended collateral venous network on the abdominal surface (Arnheim; Charles; Engel et al.). More rarely, obstruction to venous return is severe enough to produce ascites and edema of the lower extremities. Fever may be due to liberation of pyrogens from the tumor. Pain in the legs or back is infrequently seen with retroperitoneal tumors (Braasch and Mon); when present, it does not necessarily indicate unresectability of the mass. Large mesodermal extrapancreatic tumors of the retroperitoneum have been known to associate with hypoglycemia through an imperfectly known mechanism (Nissan et al.), but this association has not been reported in retroperitoneal teratomas, regardless of tissue composition.

Roentgenologic and Laboratory Examination. From their origin in the retroperitoneum, teratomas tend to cause downward displacement of the kidney, upward deviation of the liver, and anterolateral displacement of the bowel (Charles). The resulting radiologic images have proved so helpful in the diagnosis that the physical signs have received only scanty consideration (Pantoja et al.). Often mentioned is the presence of well organized calcification (Arnheim), bones, or teeth. Such images are virtually diagnostic of a teratoma. Intravenous pyelography is helpful to detect kidney involvement, distortion of the pelvis and ureters, and compression or elongation of the calyces and infundibula. Barium contrast studies of the intestine are usually not indicated. Pneumoperitoneum was traditionally advocated to distinguish intraperitoneal from retroperitoneal tumors, although its usefulness was not uniformly accepted. In selected cases, carbon dioxide insufflation of the retroperitoneal space will help to outline the position and extent of the tumor relative to neighboring structures. Computerized tomography (CT) has largely superseded many of these procedures in recent years. The heavy amounts of irradiation that this procedure requires may limit its application in the very young patient. Excretory pyelography remains the single most valuable study in children with retroperitoneal tumors (Snyder et al.; figs. 92, 93). Technics using ultrasound may be useful, but not enough experience is available in the diagnosis of retroperitoneal teratoma by sonography.

In many institutions, it has become routine to perform skeletal surveys in children with retroperitoneal tumors. Since a large proportion of these patients bear malignancies capable of having distant metastases at the time of initial examination, such as neuroblastoma, this conduct is fully warranted. The same may be said for obtaining routine needle biopsies of bone marrow, or of skeletal lesions, if present. Urinalysis and peripheral blood count should be routine; urinary excretion of catecholamine metabolites should be investigated. Justification of the routine performance of these procedures derives from the well known fact that neuroblastoma and Wilms' tumor constitute the vast majority of pediatric retroperitoneal neoplasms. In contrast, diagnostic procedures involving retrograde catheterization of the urinary tract are not usually recommended, because of the risk of spreading tumor cells when the kidneys may be involved. In particular, opposition has been voiced against needle biopsy of retroperitoneal tumors (Snyder et al.). Besides the real dangers of spreading tumor cells, introducing infection, and causing accidental severe bleeding, the diagnostic accuracy of this procedure is compromised by the scantiness of the sample; this limitation seriously curtails the usefulness of the procedure in tumors of composite histology, outstanding examples of which are teratoma and Wilms' tumor. Additional useful procedures include venography of the inferior vena cava, lymphangiography, and retrograde aortography.

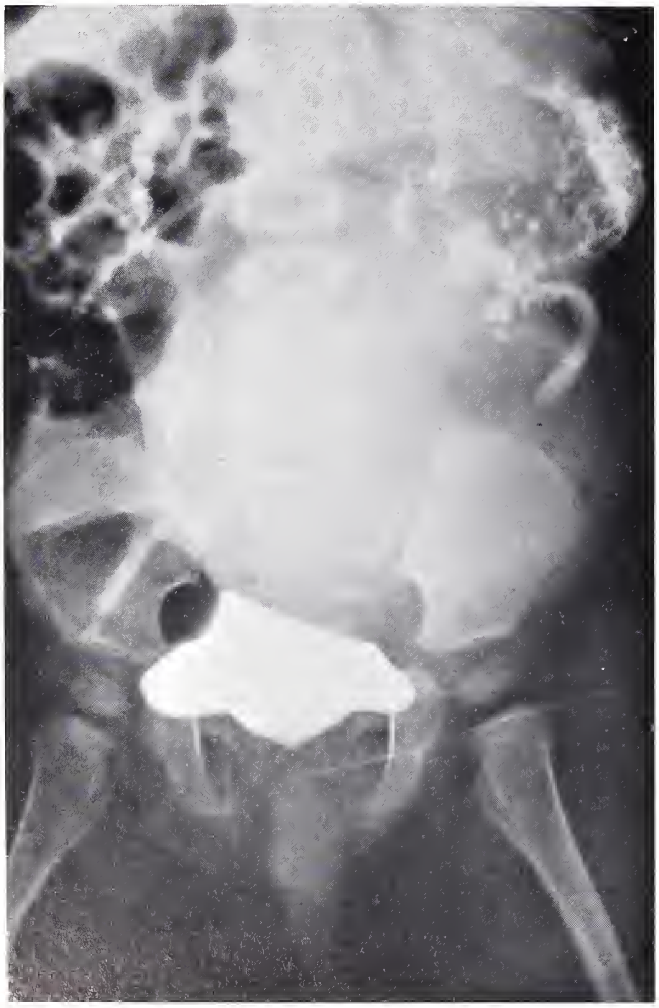


Figure 92
(Figures 92 and 93 from same case)
RETROPERITONEAL TERATOMA
Pyelogram of female child with a large retroperitoneal teratoma. Anterolateral displacement of ureter at pelvic outlet and compression of the bladder are apparent on the anterior view. (Courtesy of Dr. E. Franken, Indianapolis, IN.)

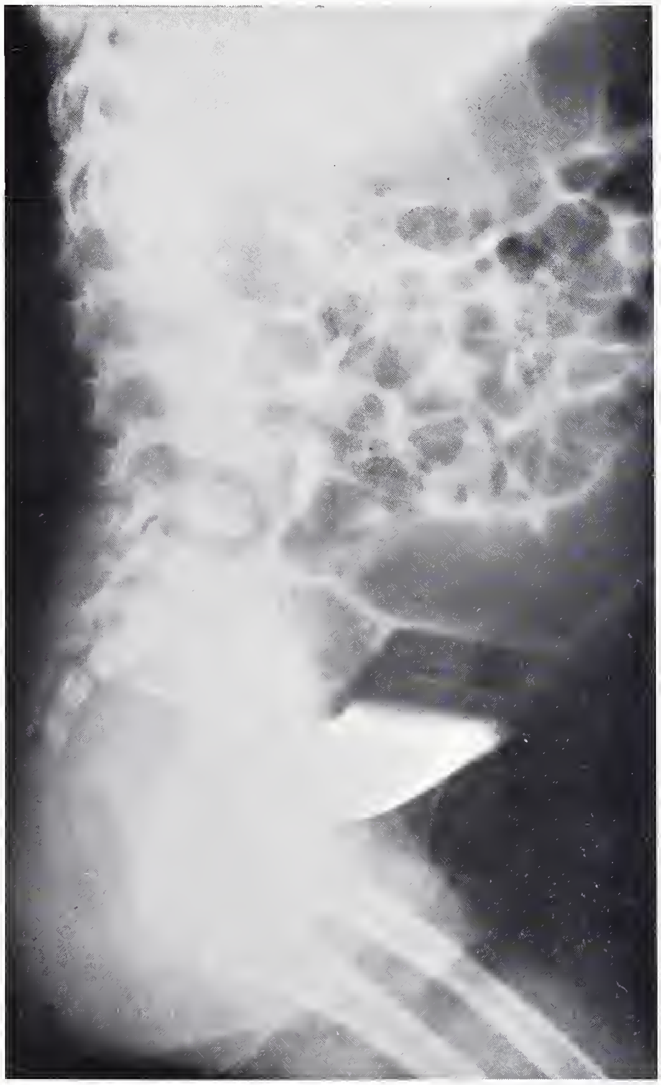


Figure 93
RETROPERITONEAL TERATOMA
Lateral view shows displacement of bowel and bladder compression. (Courtesy of Dr. E. Franken, Indianapolis, IN.)

Gross Appearance. These tumors are often encapsulated and composed of cystic and solid areas. As is commonly seen in teratomas, the benign lesions are often multicystic (pl. V-A; fig. 94). The cysts may contain hair and keratinous debris. These lesions may range in size from a few centimeters to huge masses that displace all adjacent structures and have reached the amazing weight of 26 pounds (Pantoja et al.). Necrosis and hemorrhage are apt to be found in malignant tumors, but only by histopathologic examination is it possible to determine the benign or malignant nature of these neoplasms. Gross confinement appears less distinct in malignant teratomas, which tend to be multilobated, solid, and ill-delimited, with areas suggesting extracapsular spread.

Microscopic Appearance. The benign cases cannot be distinguished histologically from teratomas of other sites. Calcification and ossification (Banerjee et al.; Chute et al.; Palumbo et al.) are often present, as are cysts lined by a variety of epithelia, including squamous epithelium, glandular-like cylindrical epithelium, and ciliated cells. Foci of ectodermal glial tissue, and tissues of endodermal and mesodermal origin are regularly seen (pl. V-B; figs. 95–99). Immature foci that resemble stages of early embryonic organogenesis should be carefully examined, for these tissues are potentially malignant.

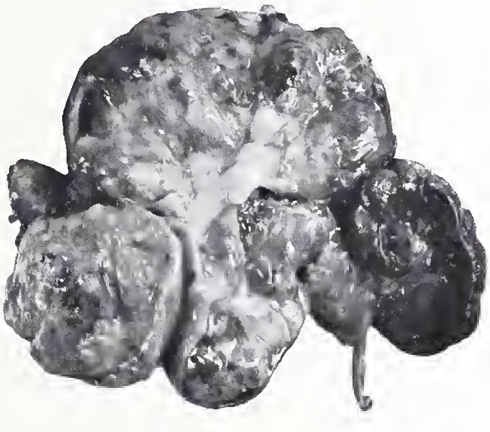
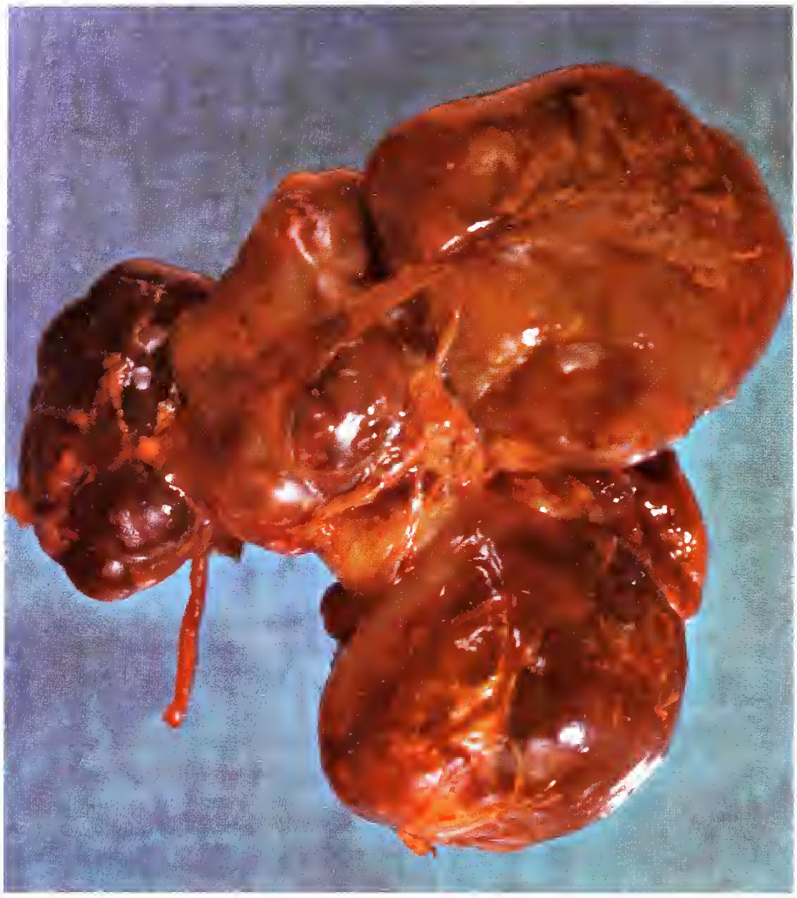


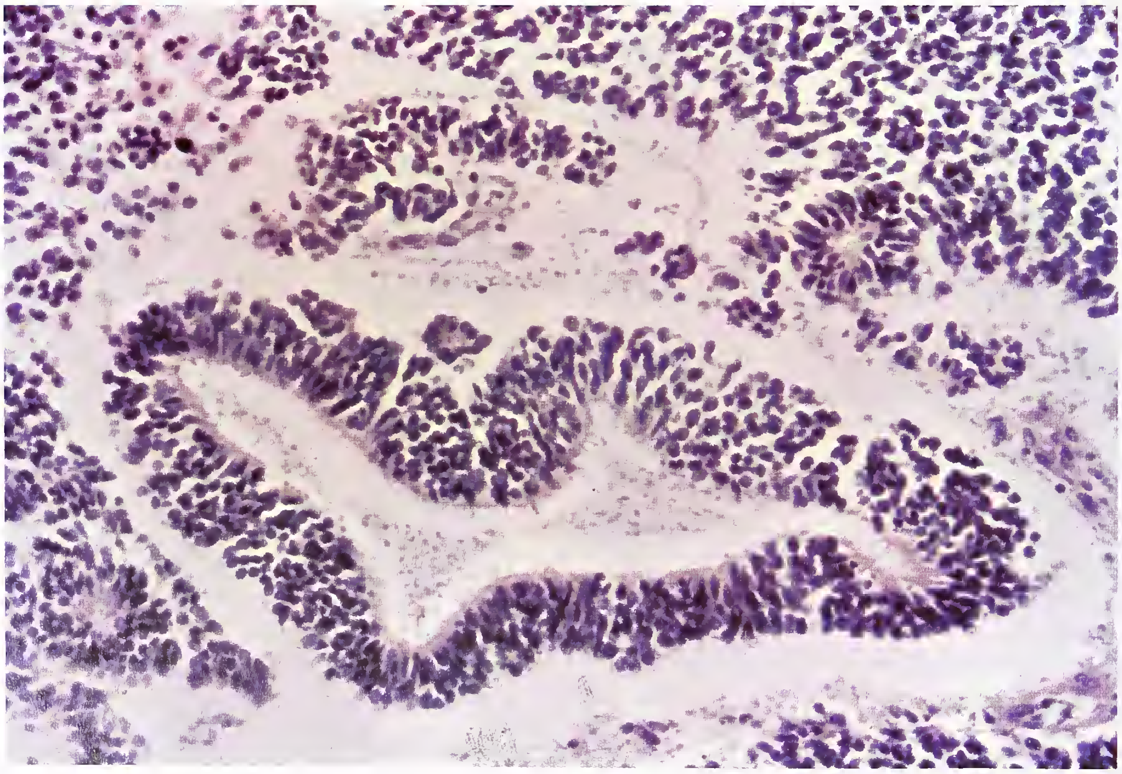
Figure 94
RETROPERITONEAL TERATOMA
Multilobulated, cystic and solid, congenital retroperitoneal teratoma. Intimate attachment to the kidney, which appears intensely congested, simulated a renal neoplasm necessitating complete nephrectomy.

Malignant tumors may contain zones of "germinal" tumor in a manner entirely comparable to other extragenital teratomas (figs. 100, 101). Since the lymph nodes in the retroperitoneal space are placed in the drainage path of the gonads, it is necessary to exclude the presence of gonadal primary tumor, as discussed under Differential Diagnosis. The possibility that a germ cell tumor may arise as a primary neoplasm in the retroperitoneal space is also discussed in the same section. Other histologic patterns may be present in malignant cases. Carney described the presence of Wilms' tumor and renal adenocarcinoma in a large retroperitoneal tumor of a 41 year old man. This patient had had an orchiectomy for testicular teratoma four and one-half years previously, thereby casting doubt on the primary nature of the tumor. Circumstantial evidence adduced in favor of its primary origin in this area was the fact that it contained malignant renal tissue, a feature virtually nonexistent in testicular teratomas, but known to be present in occasional instances of retroperitoneal teratoma (Willis). Carney speculated about the possible influence of pronephros-inducer substances evoking the differentiation of teratoma cells into renal tissue. Another uncommon microscopic pattern in a malignant retroperitoneal teratoma was interpreted as adenocarcinoma of bronchial epithelium (Lie). The case was a rapidly fatal teratoma of a 22 year old man that gave rise to extensive peritoneal seeding and liver metastases. In spite of the tendency to

PLATE V
RETROPERITONEAL TERATOMA



A. Histologic Grade 3 teratoma, clinically confused with primary renal neoplasm, in a two day old girl. Kidney and ureter are closely related to, but independent from, the mass. Tumor parenchyma characterized by cystic and solid areas.



B. Immature neuroectodermal tissue in a retroperitoneal teratoma that metastasized to adjacent lymph nodes. X410.

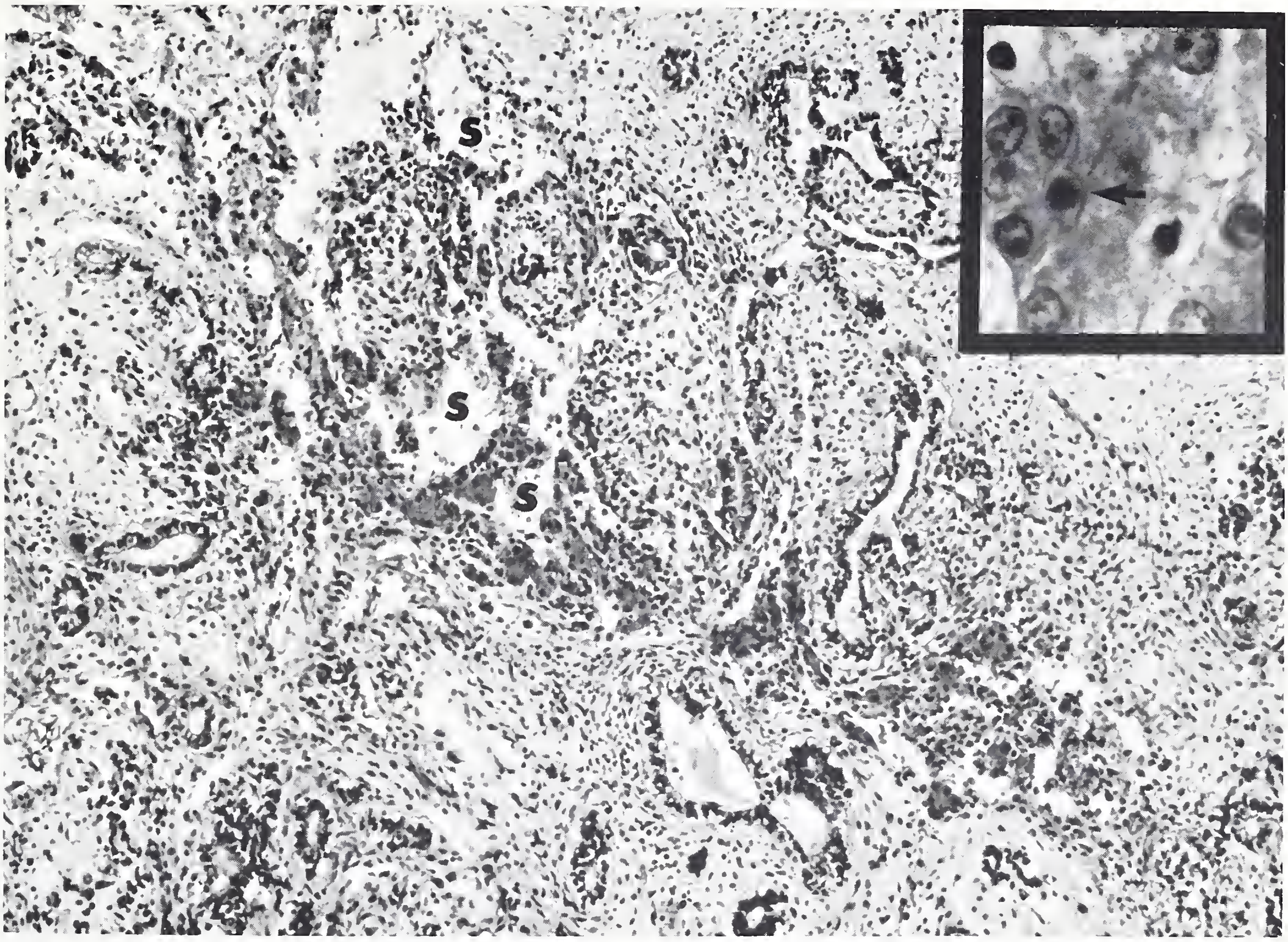


Figure 95
RETROPERITONEAL TERATOMA
Immature tissues of embryonic appearance in benign retroperitoneal teratoma. Cell cords separated by sinusoidal distended spaces (S) reproduce the structure of immature liver. X150. Inset: Liver cells show evidence of bile production (arrow). X350.

report the uncommon patterns, retroperitoneal teratomas do not appear to differ from teratomas of other, more common sites. Thus, embryonic-appearing tissues in general should be regarded as potentially malignant. When these tissues are abundant and form a large proportion of the tumor, the likelihood of its behaving aggressively is consequently increased. In personally examined cases with metastases to lymph nodes, the metastatic deposits were composed of small, dark, neuroblastic elements and tubule-forming taller cells apparently representing primitive neuroectodermal epithelium (pl. V-B). These elements were set amidst areas of myxoid tissue with the appearance of primitive mesenchyme, and tubular branching glands of embryonic appearance, and of uncertain, probably endodermal, derivation. Mesenchyme and glandular elements accompanied the neuroectodermal cells in some of the metastases. It is likely that neuroectodermal tissues predominate in teratomas of this location, as they often do in teratomas of other sites. Malignant behavior of this component might explain the reported association of neuroblastoma with cystic teratomatous elements (Chuahirun and Hasson). The limited experience available precludes any conclusions about the ultimate clinical behavior of the immature neural tissue in retroperitoneal teratomas; conceivably, some cases might retain a capacity for spontaneous differentiation into mature neural tissue.

Differential Diagnosis. Retroperitoneal tumors in childhood present as palpable intra-abdominal masses. Only about half of such masses are of surgical concern, but of these, the majority, or close to two-thirds, originate in the kidney (Snyder et al.). It is common knowledge that Wilms' tumor vastly dominates the pathology of intrarenal tumors in childhood, but a number of benign and malignant tumors, as well as tumor-like malformations (Gonzalez-Crussi et al.) and teratomas, may have a renal origin. Intrarenal teratomas are discussed separately in this volume (see Teratomas of the Kidney). Thus, the clinical differential diagnosis must start by careful ascertainment of the anatomic position of the neoplasm. Plain films and excretory urography often suffice to establish the intrarenal origin of a tumor. Diagnostic accuracy has markedly improved through judicious use of modern specialized technics, such as arteriography, ultrasonography, isotope renography, and computerized tomography.

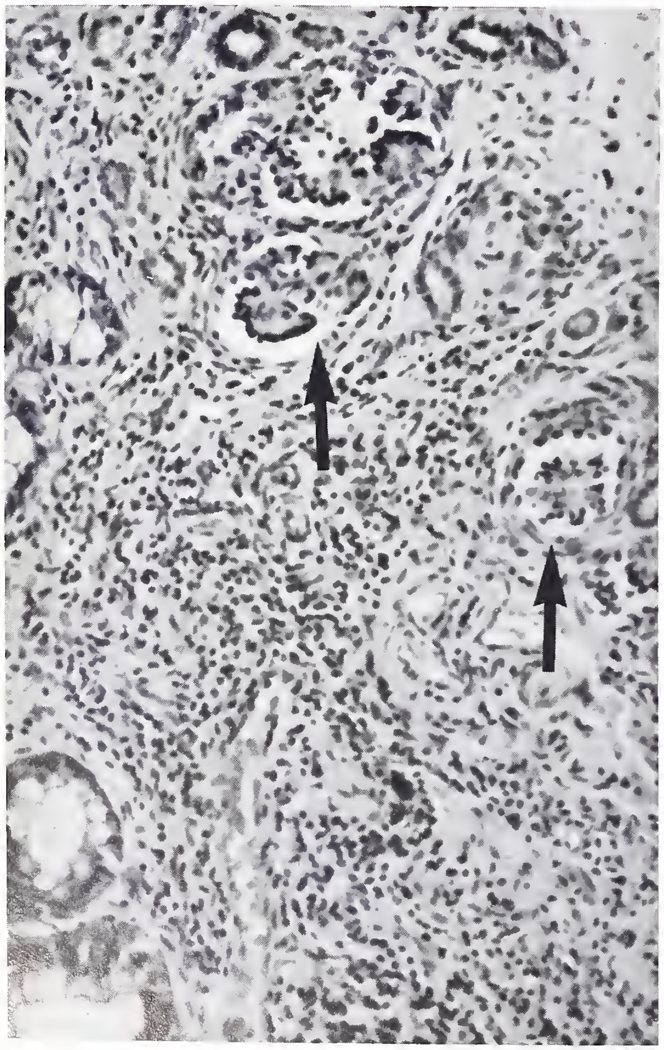


Figure 96
RETROPERITONEAL TERATOMA
Cyst lined by colonic mucosa that shows renal glomeruli (arrow) developing in the "lamina propria." X410.

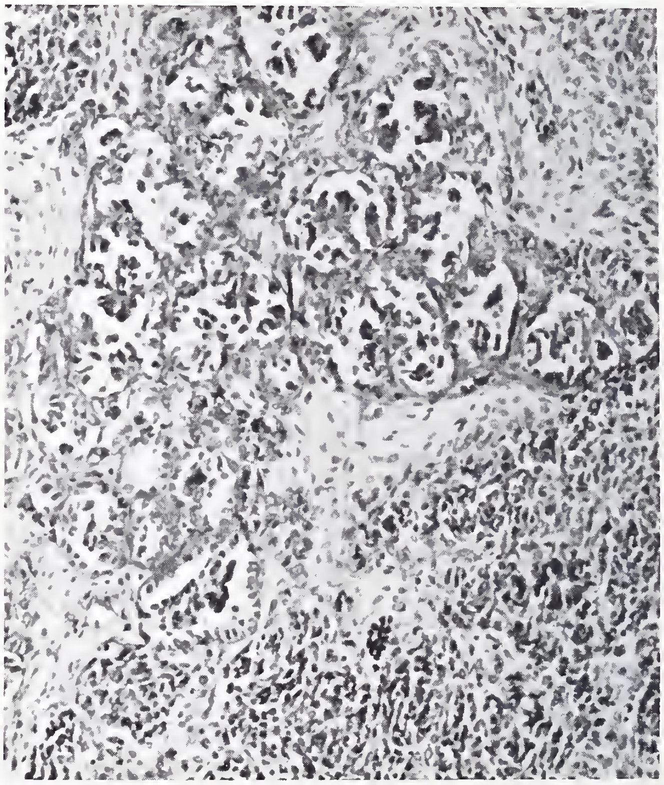


Figure 97
(Figures 97 and 98 from same case)
RETROPERITONEAL TERATOMA
Embryonic tissues of difficult characterization in malignant retroperitoneal teratoma. Epithelial and mesenchymal tissues were present in the primary tumor, but only neuroectodermal tissue was found in the metastases. X75.

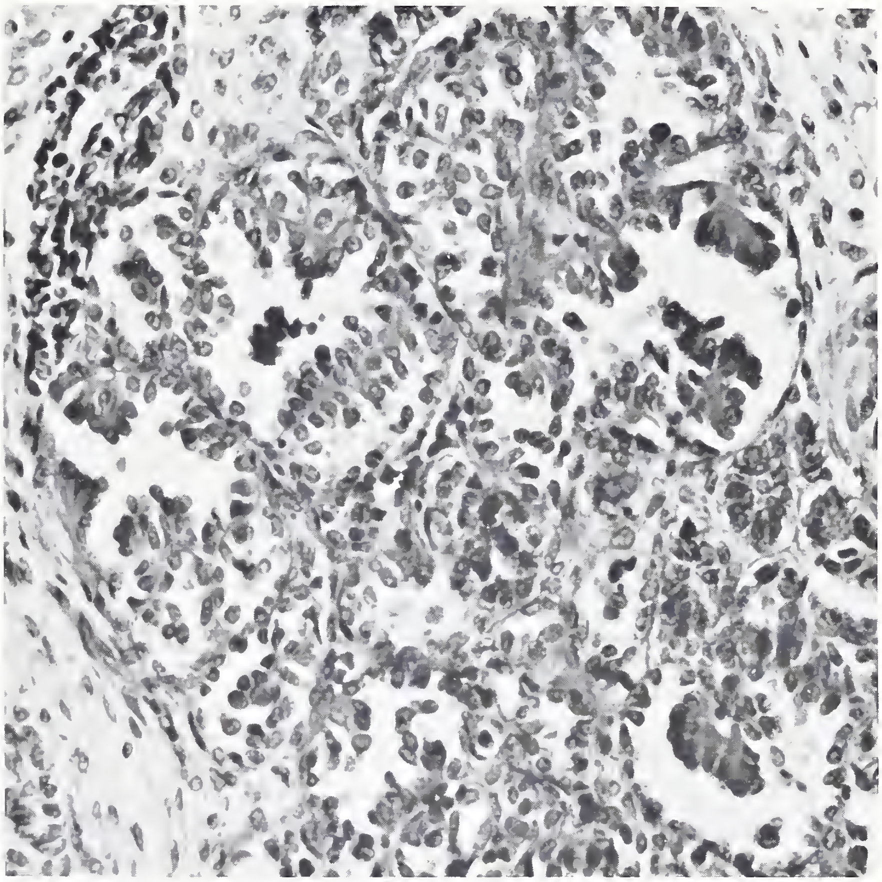


Figure 98
RETROPERITONEAL TERATOMA
High magnification of epithelial-like zone in preceding illustration shows alveolar and papillary arrangement of small cells. X375.

In spite of these advances, and due to voluminous growth or invasive behavior, it may be difficult to define the anatomic origin of the mass. In children, the two most common solid retroperitoneal tumors are Wilms' tumor and neuroblastoma. Both commonly present as abdominal mass, and roentgenographic distinction may not be straightforward. Neuroblastoma may be congenital, but is usually inapparent until after 6 months of age. Radiographically, it may be possible to trace its location to the adrenal gland or extrarenal sites, and to demonstrate fine "speckled" calcifications. Together with evidence of functional output of catecholamines by the tumor, these data often permit the diagnosis prior to histopathologic confirmation. In contrast, Wilms' tumor is uncommon during the first year of life and exceptional at birth. Its anatomic origin within the kidney is readily apparent in the majority of cases; calcification is less common and, when present, adopts a coarser pattern. Neither of these two tumors shows the organized foci of ossification or radiographic images characteristic of teeth, which may be present in teratomas. Benign teratomas are frequently multicystic, a quality that may sometimes be advantageously revealed by tomography or ultrasound. The histopathologic differential diagnosis is not a problem. Neuroblastoma is a neoplasm of exclusive ectodermal origin. Although different degrees of differentiation may be present in its cellular constituents, it remains a "monodermal" tumor. Wilms' tumor has a more complex structure, such that it may bear a superficial resemblance to teratoma. However, prominent endodermal derivatives are not a feature of Wilms' tumor, but a regular finding in teratomas, which almost always

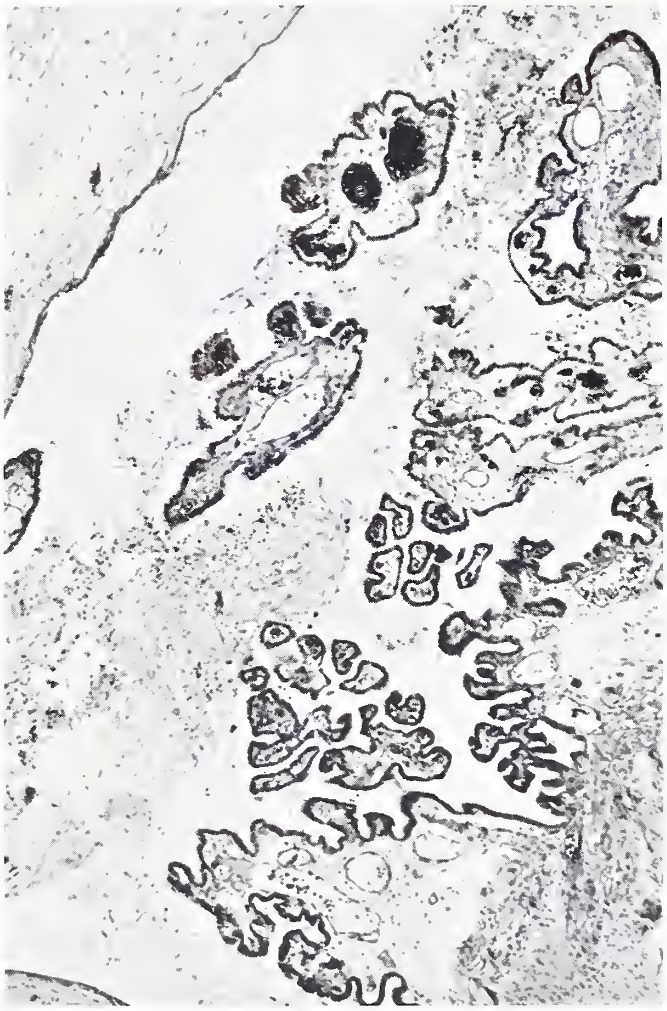


Figure 99
RETROPERITONEAL TERATOMA
Papillary structures similar to choroid plexus, projecting into the lumen of a tumor cyst. X225.

display respiratory epithelium and "colonic" type glands. Occasional instances of ectodermal differentiation in Wilms' tumor have been noted, as discussed in the section on Teratomas of the Kidney.

In adults, liposarcoma is said to be the most common tumor of the retroperitoneum (Ackerman), but in children this tumor is extremely rare. Children may develop large retroperitoneal lipomas associated with a characteristic radiolucent appearance on x-ray films (Weitzner et al.). As is true for other tumors rarely occurring in the retroperitoneum and unrelated to the kidney, such as fibromas, leiomyomas, or hemangiomas, their monomorphous histologic composition stands in sharp contrast with the heterogeneous, variegated appearance of teratomas. A pathologic condition that arises in the retroperitoneum and is structurally akin to teratomas is "fetus-in-fetu." Distinction between this lesion and a teratoma may be difficult on purely morphologic grounds, since some authorities acknowledge that a gradual transition exists between teratomas, parasitic twins, and conjoined twins (Potter and Craig). The salient clinical and pathologic features of "fetus-in-fetu" were discussed in the corresponding chapter (see Fetus-in-fetu). The arbitrary criteria of axialization and metameric segmentation were mentioned as the main features on which to base a morphologic distinction from teratomas.

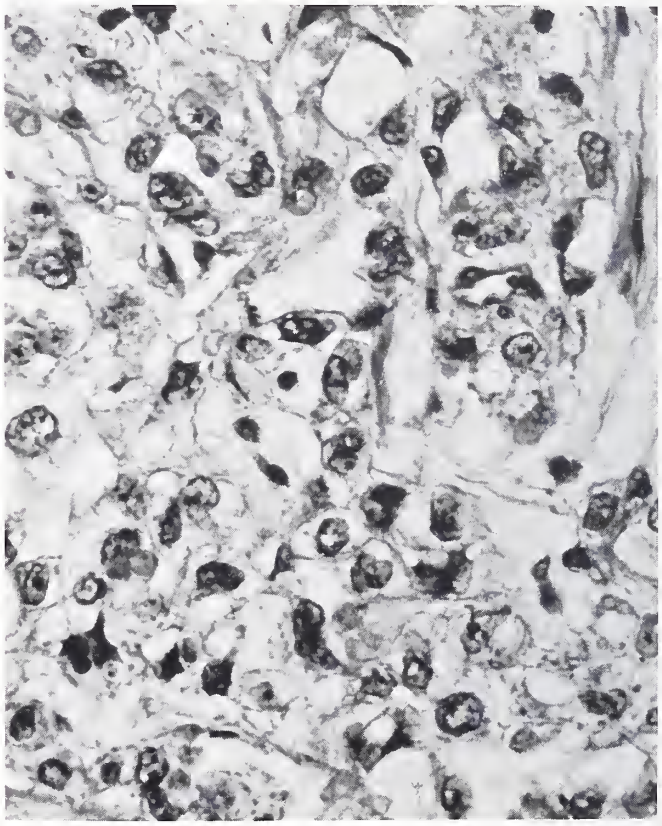


Figure 100
RETROPERITONEAL TERATOMA
Large cells of clear, vesicular nuclei with marked pleomorphism correspond to germ cell tumor (embryonal carcinoma) component of retroperitoneal teratoma. X410.

Malignant teratomas of the retroperitoneum pose special problems of differential diagnosis. Because the lymphatic drainage of the gonads is placed in the retroperitoneal space, malignant gonadal tumors often metastasize to this area. Furthermore, the metastases of a germ cell tumor may differentiate so completely as to simulate a mature teratoma (Hong et al.). Hence, one problem is to rule out a gonadal germ cell primary tumor in every instance of retroperitoneal teratoma, regardless of the latter's degree of differentiation. This may represent a formidable task, because primary testicular tumors may remain minute and clinically inapparent, while the metastatic deposits dominate the symptomatology. There are currently no set guidelines for the clinical approach to this problem. In theory, complete assurance that the testes are free of tumor can only be obtained by castration and serial sectioning of the testes at 2 mm. intervals, since a 2 mm. germ cell tumor has been known to metastasize. The impracticality of this approach needs no reiteration, and the surgical conduct has been variable. If the retroperitoneal tumor coexists with an atrophic gland, some surgeons elect to perform an orchiectomy of the atrophic gland, which is deemed more likely to harbor a tumor (Wacksman et al.). When the retroperitoneal tumor is lateralized, ipsilateral orchiectomy and biopsy of the contralateral testis have been advocated. Criticism of these procedures rests on the premise that such surgery may be too extensive, as the number of occult testicular tumors is too small to justify mutilating operations; testes of patients with extragonadal germ cell tumors, when extensively sectioned at autopsy, usually reveal no evidence of tumor, and occasionally may show scars of debatable interpretation (Johnson et al.; Wacksman et al.). Hopes for greater accuracy in the clinical diagnosis of occult testicular tumors hinges on the development of newer and more sensitive technics than have been available heretofore. Scrotal thermography, a noninvasive technic, is becoming a helpful adjunct, although its specificity is limited (Gold et al.).

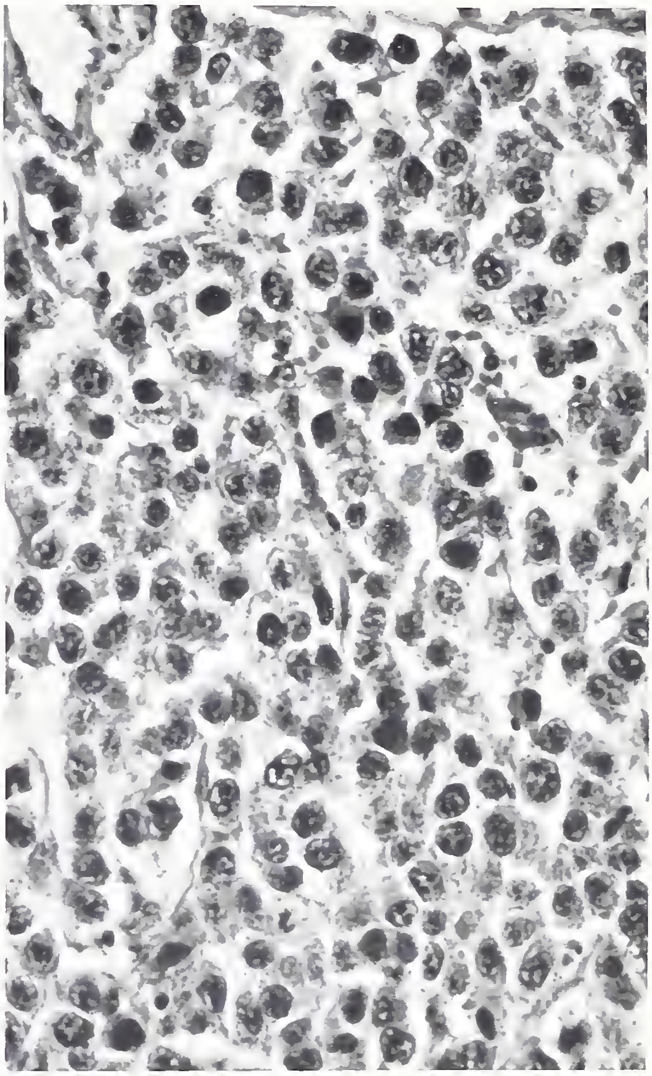


Figure 101

RETROPERITONEAL TERATOMA

Large, noncohesive, atypical round cells with the characteristic pattern of germinoma, in a retroperitoneal tumor of a 35 year old man with past history of a left testicular teratoma excised eight years previously. The possibility of metastatic origin cannot be entirely ruled out. X175.

The malignant portion of a retroperitoneal teratoma, like other extragonadal teratomas, may comprise areas of germ cell tumor. Teratomas with a yolk sac tumor component that are found in the lower retroperitoneum might represent examples of sacrococcygeal or presacral tumors with predominantly intrapelvic, cephalad growth (see Sacrococcygeal Teratomas). As discussed precedingly, a primary occult gonadal tumor should be excluded in every case of germ cell tumor located in the retroperitoneal space. However, germinomas arising de novo in this location have also been reported. Abell and associates proposed that at least one of the following criteria should be met before accepting a germinoma as primary in this anatomic area: (1) presence of nonneoplastic gonadal tissue in the tumor's capsule, or immediately adjacent to the mass; (2) encapsulated tumor with no lymph nodal involvement; or (3) high retroperitoneal tumor that may have adjacent lymph node involvement, but without metastases in the lower aortic, iliac, or pelvic lymph nodes. The histopathology of such tumors has been indistinguishable from testicular seminomas. Accordingly, the microscopic differential diagnosis should not represent a problem. If these masses originate in displaced germ cells, it is reasonable to expect germ cell tumors of mixed histologic type as they occur in the gonads. Germ cell tumors of presumed retroperitoneal origin, however, have uniformly been seminomatous in type.

Prognosis. Malignancy was seen in 10 percent of the 58 cases reviewed by Palumbo and associates and in 6.8 percent of the retroperitoneal teratomas of pediatric patients collected by Arnheim. It has been stated that the structural complexity of retroperitoneal teratomas determines an almost limitless spectrum of malignant possibilities (Pantoja et al.). However, in view of the paucity of observations and the low incidence of malignancy, it has been very difficult to determine the structural identity of the most frequent type of malignant component. Of the 25 cases studied by Sariñana and associates, only 1 was malignant; in 22 patients surgical excision was curative, and 3 patients died: 1 with malignant disease, 1 due to peritoneal infection, and 1 to intestinal infarction. Of the 31 surgically treated patients reviewed by Arnheim, 9 died from complications incidental to attempted surgical removal.

Treatment. Surgical excision, the primary form of treatment, may be relatively easy with a well confined, small retroperitoneal tumor. A large and adherent mass in this location, however, poses technical problems of difficult solution (Hansmann and Budd; Hartwell). Occasionally, resection is achieved in two stages. The initial operation is designed to relieve acute symptoms, such as those due to intestinal obstruction, thereby facilitating removal of the tumor at a later time (Keramidas and Voyatzis). Retroperitoneal masses in children are most often approached transabdominally, instead of using the lumbar approach, since the former allows wider exposure, visualization of both sides of the retroperitoneal space, and easier control of the venous drainage; a thoracoabdominal incision has been used for exceptionally large masses (Braasch and Mon). Complete excision is the aim of treatment. The decision to employ chemotherapy or radiation therapy, a conduct confined to tumors of proved malignant characteristics, is the domain of the oncologist. This decision is largely influenced by the type of malignant tissue present in the teratoma.

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INTRACRANIAL TERATOMAS

SYNONYMS AND RELATED TERMS: Atypical teratoma; germinoma; ectopic pinealoma; heterotopic pinealoma; normotopic pinealoma; germ cell tumor; intracranial teratoma; teratoid tumor; intracranial choriocarcinoma; embryonal carcinoma; intracranial endodermal sinus tumor; congenital intracranial teratoma; teratoma of the pineal body.

Intracranial teratomas are rare; their incidence has been estimated at 0.5 percent of all intracranial tumors (Zülch). However, this figure is appreciably higher when infants and young children are included in the series; Russell and Rubinstein estimate that the incidence may then increase to about 2.0 percent. Partly, the discrepancy is explained by the fact that children with a congenital intracranial teratoma rarely survive beyond one year of age (Jellinger and Sunder-Plassmann), and most die in a few days or weeks (Arseni et al.; Greenhouse and Neubuerger; Hirsch et al.; Hübner; Jellinger and Sunder-Plassmann; Lehman and Torres-Reyes; Morelli; Vraa-Jensen; Wagner et al.). There is also a suggestion that populations in certain geographic areas, particularly in the Far East, may exhibit an inordinately high number of cases of this nature. In Japan, pineal tumors represent close to 4 percent of all primary intracranial neoplasms (Araki and Matsumoto; Ito; Rubinstein).

Intracranial teratomas commonly arise in the pineal area. There has been, however, much confusion surrounding the terms used for tumors of this anatomic site. Some historical considerations may help to dispell the remaining uncertainty. It has long been known that tumors arising in the pineal are often made up of large, pale-staining cells. Based on the work of embryologists at the beginning of the century, such cells were mistakenly interpreted as embryonic parenchymal cells of the pineal ("pinealoblasts"), and the tumors named "pinealoblastomas," or "pinealocytomas," depending on the degree of admixture with cells thought to more closely resemble pinealocytes. "Pinealoma" was, during the thirties, a generic term for tumors believed to arise from pineal parenchymal cells. Credit is usually given to Dorothy Russell for the recognition of pineal tumors that are histologically identical to seminoma of the testis (or dysgerminoma of the ovary). Thus, it became apparent that "pinealocytoma" or "pinealoblastoma" should be terms reserved for tumors whose origin from pineal parenchymal cells has been reasonably well documented. Proof of such ancestry has rested on histochemical stains and, more recently, on ultrastructural studies, as discussed by Rubinstein and by Russell and Rubinstein. Our concern here is to emphasize that a group of tumors, though arising within the pineal, are composed of cells unrelated to this tissue, and identical to testicular seminoma cells. Russell coined the term "atypical teratoma" to underline the fact that such tumors are no different from germ cell tumors occurring in other locations. As previously stated in this volume (see Classification of Gonadal and Extragonadal Teratomas. Use of Terms in Pathologic Diagnosis), there are reasons to believe that all germ cell tumors are ultimately interrelated, and this close relationship has been conceptualized in the belief that all are teratomatous in nature ("one-sided" teratomas). Rubinstein has more recently endorsed the use of the term "germinoma," proposed by Friedman, as short, euphonic, descriptive, and easily qualified according to the location of the tumor by mere addition of the appropriate name of the anatomic site. Thus, in the ensuing discussion, the term "germinoma" will be used for those tumors of germ cell derivation, which are structurally indistinguishable from testicular seminoma or ovarian dysgerminoma. Embryonal carcinoma, choriocarcinoma, and yolk sac tumor are neoplasms whose ancestry may be traced to germ cells. However, because of the recent realization that important diagnostic and prognostic differences attach to these histologic variants, it is desirable to use terms which denote the presence of such microscopic patterns in a germ cell tumor. Such will be the practice in this section. The term teratoma will be meant to denote a tumor of trigerminal tissue composition. The existence of neoplasms that show a mixed germ cell pattern, or combinations of germinoma and teratoma, in the sense just defined, is well recognized (Rubinstein; Russell and Rubinstein). Such tumors are aptly named by descriptive designations in which the mixed nature of their histologic structure is brought into focus.

Germ cell tumors and teratomas arising inside the skull originate most commonly in the pineal or parapineal area. Use of the term "pinealoma" for all supraquadrigeminal neoplasms, not uncommon in the surgical literature, should be discouraged. "Ectopic pinealoma" further compounds the dismal terminologic chaos; it generally means an intracranial germinoma that has arisen away from the common site of origin, without involvement of the pineal itself. Over 50 percent of the growths affecting the pineal body are teratomas or germinomas (Soas). Another frequent location is the hypothalamus. Very often, by the time the pathologist examines the specimen the tumor has grown into the hypothalamus, floor of the third ventricle, and pituitary fossa, so that determination of the exact site of origin is not possible. Teratomas also arise, in decreasing order of frequency, in the region of the third ventricle, pituitary fossa, and posterior cranial fossa, usually in the midline plane (Rubinstein; Russell and Rubinstein).

Clinical Features. Intracranial germinomas as well as typical teratomas occur preferentially in the first two decades of life; both are seen more commonly in males. However, this preponderance of male individuals is not documented for intracranial teratomas discovered in the newborn infant. Hirsch and associates were able to find reports on 55 cases of neonatal intracranial teratoma up to 1977, most of which were seen in female infants. The neonatal intracranial teratomas constitute a distinct clinicopathologic entity. Greenhouse and Neubuerger recognized three characteristic clinical patterns. In the first one, cranial enlargement occurs abruptly from two days to three months after birth. In this group of infants the tumor tends to be small, and situated in such a way as to occlude the ventricular pathways and produce hydrocephalus. A second group of children are born alive, but with enlarged heads. Survival periods ranged from one-half hour to nine weeks. At autopsy, none of these children had a well confined tumor, and the possibility of surgical excision was judged almost nil, as all had extensive replacement of brain substance by tumor. In a third group of cases there was massive intrauterine growth, and the head was sufficiently enlarged to cause obstetric difficulties. These infants were either stillborn or died soon after birth; their tumors were themselves voluminous, or so situated as to cause severe intrauterine hydrocephalus.

Beyond the neonatal period, tumors of the pineal region, regardless of histologic type, manifest as intracranial masses that give rise to neurologic, neuro-ophthalmic, and endocrinologic syndromes. Upward-gaze palsy is probably the single most common manifestation. When present, the pupillary reflexes tend to be abnormal; in conjunction with the mentioned upward-gaze palsy, they form part of Parinaud's syndrome. Bell's phenomenon, the upward tonic deviation of the eyes when the patient makes a forced eyelid closure, may also be seen (Bell and McCormick). Paralysis of convergence is sometimes present. This is characterized by failure of eye convergence with crossed diplopia when the patient views a near target, but absence of paresis of the medial recti on lateral gaze. Collier's sign, consisting of pathologic retractions of the eyelids (the "posterior fossa stare") when the patient looks straight ahead, is rarely present and usually associated with paresis of upward gaze. Because the tumors are situated above the aqueduct of Sylvius, obstruction and hydrocephalus may supervene. Papilledema occurs in 56 percent of the patients; it is thus an important sign, although by itself has no localizing value.

Prominent among the endocrine manifestations of pineal tumors are abnormalities of sexual maturation. Precocious puberty associated with tumors of the pineal region is said to occur only in boys (Axelrod). David and co-workers concluded that precocious puberty occurs in 43 percent of male patients with pineal tumor and in 50 percent of those with a teratoma, but apparently this term encompassed all germ cell tumors of this region. Because there is a bias in favor of reporting cases associated with endocrine syndromes, it is likely that the actual frequency of these disorders is much lower than suggested by analyses of series of published cases. Axelrod gives the following three theoretic reasons to account for precocious puberty in boys with tumors of the pineal region: (1) The pineal exerts an antigonadotropic effect, possibly related to secretion of melatonin or other compounds. Destruction of the pineal gland by tumor might release the gonads from this inhibitory influence and lead to precocious sexual development. (2) The expanding tumor exerts hypothalamic compression, thus destroying or damaging inhibitory diencephalic areas that normally restrain the secretion of gonadotropins. (3) The tumor itself is capable of secreting "ectopic" gonadotropins.

Difficulties in the technics for identification and quantitation of circulating melatonin have stood in the way of adequate support for the first two theoretic explanations mentioned above. The third one, that the tumors of the pineal region can secrete HCG, has been verified in some cases (Vaitukaitis); tumors with this ability are usually germinomatous in type. The paucity of cases studied thus far has made it difficult to establish a correlation between histologic type and secretory capacity. On the other hand, there are pineal tumors that associate with hypogonadism: the onset of puberty is delayed, or, after puberty, secondary sexual characteristics regress. These effects may be due to hypothalamic compression, to systemic illness and its consequent general debilitation, or, if the tumor contains parenchymal pineal cells, one may hypothesize the release of excessive quantities of an antigonadotropic factor (Kitay; Sano; Schmidek).

The classical triad usually emphasized (Bell and McCormick; Camins and Mount) consists of visual disturbance, diabetes insipidus, and hypopituitarism. Because of their proximity to the pituitary gland and hypothalamus, suprasellar germinomas are apt to result in growth retardation, disorders of sexual maturation, aberrations of thermoregulation, and alterations of consciousness. Abnormalities of water balance characteristic of diabetes insipidus were seen in only 4 of the 58 cases reviewed by Camins and Mount. On the other hand, a greatly increased water intake may be present months or years before any other manifestation occurs. In the nine patients reported by Simson and associates, visual disturbance and diabetes insipidus were the earliest and most frequent clinical manifestations. When diabetes insipidus occurs in association with a tumor of the pineal region, it generally indicates extension of the tumor to the hypothalamus and pituitary. This may occur as direct metastatic implantation or as contiguous growth of the tumor through the floor of the third ventricle.

Hypopituitarism is the least well studied part of the diagnostic triad. It occurs as anterior pituitary insufficiency, but hypogonadism, growth retardation, or hypoadrenocorticism are all too often said to be manifestations of anterior pituitary failure without giving firm criteria or the evidence for such an affirmation. Such manifestations could just as well be due to nonspecific effects of systemic illness, to superimposed disease, or to hypothalamic-pituitary dysfunction. Nonetheless, pineal tumors have been reported that were associated to ACTH deficiency (Puschett and Goldberg). This complication, with its attendant adrenocortical insufficiency, may be life-threatening. Hutchinson and associates found luteinizing hormone-like material in a tumor of a 7 year old boy with precocious sexual development; the patient had a normal pituitary fossa by x-rays. Early puberty also appeared in a boy of the same age described by Bruton and associates. A teratoma with areas of embryonal carcinoma, "germinoma," and choriocarcinoma was found in a parapineal position. Hormonal assay showed that large amounts of chorionic gonadotropin were present in urine and tumor tissue. In another case (Gerstley et al.) precocious puberty was noted, but the hormonal disturbances may have resulted from encroachment upon neuroendocrine structures rather than by direct endocrine secretion from neoplastic tissues. It remains hypothetic to postulate that a decrease of the inhibitory activity that the pineal gland exerts over the gonads accounts for precocious puberty in such cases (Sano).

Roentgenologic and Laboratory Examination. A host of specialized neurodiagnostic technics have proved their value in the detection of intracranial teratomas. Plain x-ray films of the skull are sometimes suggestive of the diagnosis when a calcified shadow is revealed within the tumor (Crosby). Depending on the size of the mass, roentgenologic findings may include widened cranial sutures, craniofacial disproportion, or only minimal abnormalities. In contrast to pituitary adenomas and craniopharyngiomas (tumors that often cause visible destruction of the sella turcica), only 14 of 58 cases of "germinoma" reviewed by Camins and Mount showed sellar alterations detectable on plain skull films. When the intracranial pressure is normal, air encephalogram, or positive contrast ventriculogram, is a valuable test. Suprasellar tumors commonly cause obliteration of the optic and infundibular recess that is advantageously shown by this technic. The floor of the third ventricle is visualized, and its obliteration or elevation well outlined by contrast studies. Intracranial angiograms characteristically show deviation of the main cerebral arteries by the tumor, a fine vascular network ("tumor stain"), and early venous shunting. During arterial and early venous phases, the homogeneous vascular blush may acquire a reticular appearance; this angiographic image can sometimes be correlated with the multicystic gross appearance of the tumor.

Computerized tomography (CT) is currently regarded as the single most important method of x-ray diagnosis of pineal tumors (fig. 102). Its principal merit lies in its ability to resolve soft tissue structures that differ from each other in density only slightly. Tumors that contain cystic areas, such as teratomas, are lesions in which the pathology can be accurately predicted by CT. The morbidity of this method is lower than that of angiography or pneumoencephalography, since it is noninvasive. It is the method of choice for the tumors under discussion; however, reports of failures to uncover the presence of intracranial teratomas by CT scanning call for better judgment in the use of this technic (Brooks et al.). CT is said to have definite limitations in the

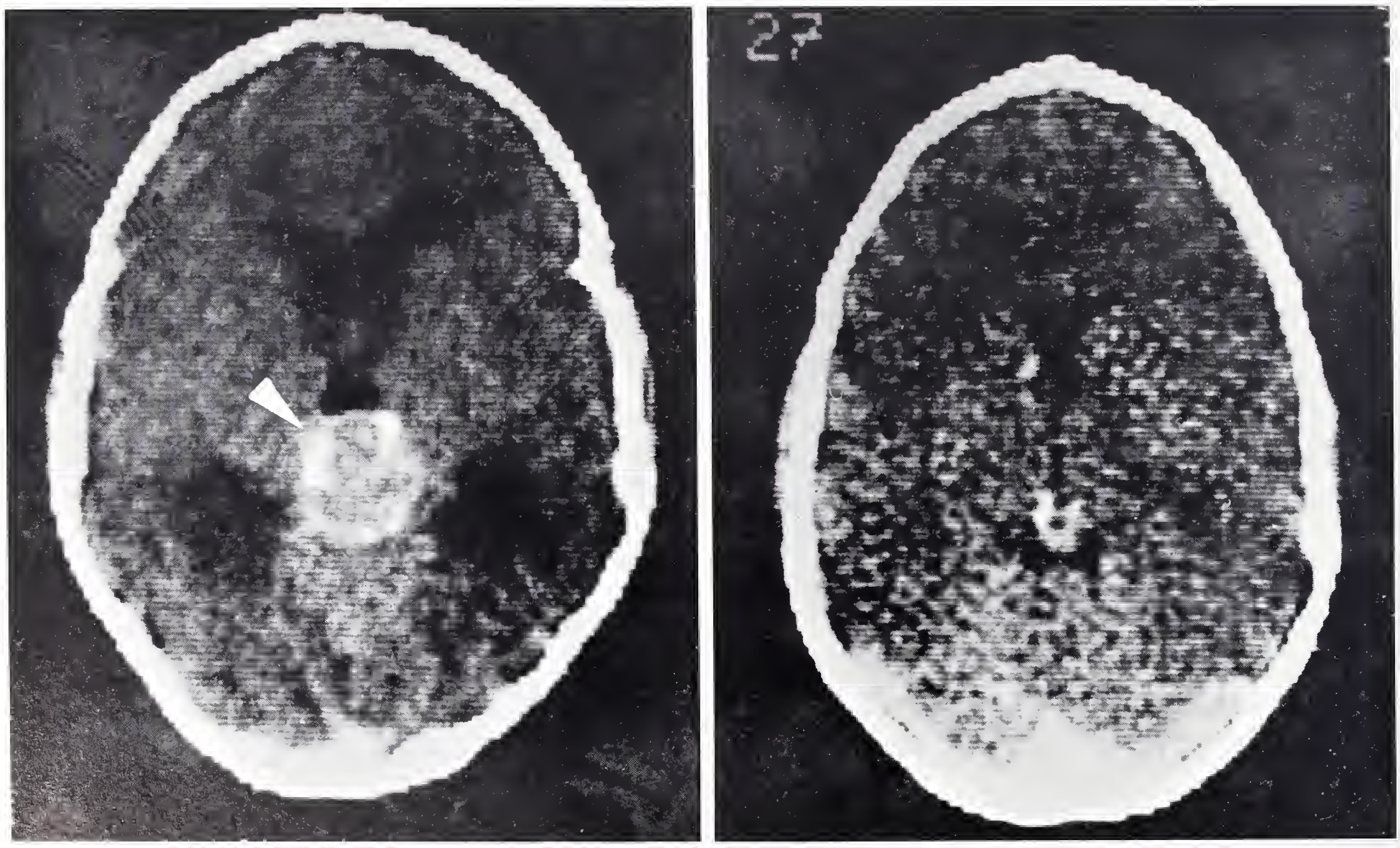


Figure 102
INTRACRANIAL TERATOMA

Computerized tomography of germinoma of the pineal area before and after radiotherapy. Note that ventricular dilatation has regressed post-therapy. (Courtesy of Dr. A. J. Altman. From Altman, A. J. and Schwartz, A. D. Malignant Diseases of Infancy, Childhood and Adolescence. In: Major Problems in Clinical Pediatrics, Vol. 18. Philadelphia: W. B. Saunders Co., 1978.)

detection of neoplasms of the posterior fossa and perisellar regions, areas in which pneumoencephalography is particularly useful (Gawler et al.). Another recent innovation in the diagnosis of intracranial tumors is the use of radioisotopic scintiscan. Technetium, indium, or ytterbium all have negligible untoward effects and have been used advantageously in the diagnosis of intracranial teratoma (Takaku et al.), which may appear as an area of excessive abnormal activity. Van Houten and associates recently reported an intracranial teratoma producing a negative defect on scintiscan, and discussed the literature.

The clinical chemistry laboratory has a prominent place in the diagnosis of intracranial teratomas. Abboud and Laws reviewed the problems of laboratory diagnosis in patients who manifest intracranial lesions with endocrine dysfunction. Axelrod states that an endocrine evaluation is imperative in all patients with tumors of the pineal. and chiasmal regions. As already stated, adrenocortical insufficiency is potentially fatal and assessment of the adenohypophyseal reserve may be crucial both to diagnosis and therapy. To assess adrenocortical function may require measurement of plasma cortisol levels and ACTH reserve by metyrapone test. Gonadotropin evaluation requires determination of plasma testosterone in males and LH and FSH levels in females. The clinical laboratory will also be useful in evaluating thyroid function and prolactin secretion as part of the estimate of adenohypophyseal reserve. The management of patients with diabetes insipidus calls for simultaneous determination of osmolality and sodium concentration in serum and urine specimens; failure to concentrate the urine in response to serum hypertonicity is diagnostic, and correction of the abnormality by administration of vasopressin establishes the intracranial, nonnephrogenic origin of the disease (Axelrod).

Interesting prospects exist for the future clinical laboratory diagnosis of pineal tumors. Melatonin is a substance (5-methoxy-N-acetyltryptamine) synthesized in the pineal by methylation of N-acetylserotonin, through the action of an enzyme that exists only in this gland. Synthesis of melatonin has been reported in the metastases of an intracranial germinoma (Wurtman and Kammer). At the present time it seems confusing that a tumor not derived of pineal parenchymal cells should be able to synthesize products considered to be the exclusive attribute of pineal cells. However, assays of extracranial germinomas have not been carried out and it is possible that identification of specific biochemical compounds might gain prominence as a means of ascertaining the biosynthetic ability of different tumors. Currently, the biochemical diagnosis in cerebrospinal fluid specimens lacks such fine discriminating potency. Jordan and coworkers recently studied the concentration of various hormones in the cerebrospinal fluid of patients with various neurologic disorders and with brain tumors. They concluded that an elevated adenohypophyseal hormone concentration in the spinal fluid correlates with suprasellar extension of a tumor, but is not specific for any tumor type. A number of tumor "markers" are currently under investigation. A review of CSF substances potentially predictive of central nervous system tumors, such as enzymes and polyamines, was presented by Seidenfeld and Marton. Embryo specific proteins, such as alpha fetoprotein, or other "markers" of embryonic tumors may be expected to be useful in the diagnosis and monitoring of the prognosis of germ cell tumors. Cytologic examination of the spinal fluid, though fraught with limitations, acquires importance to diagnose tumors whose biopsy is often impracticable; improved results may follow the use of concentrating methods.

Gross Appearance. The ease with which these tumors replace neighboring structures has been alluded to before. The characteristic variegated appearance of teratomas is also the attribute of those arising as intracranial primary tumors; cystic and solid areas are commonly noted, with the cysts containing fluid of diverse composition (pl. VI-A; figs. 103–105). Areas of "germinoma" often tend to have a soft consistency and a homogeneous white hue. Necrosis and hemorrhage may be readily apparent. Because teratomas tend to occlude the pathways of cerebrospinal fluid flow, some degree of hydrocephalus is almost always present.

The congenital form of intracranial teratoma shares these gross attributes, but it may be massive (fig. 104). Several illustrative examples are available in which almost the totality of the cerebral hemispheres was replaced by tumor tissue (Greenhouse and Neubuerger; Sheline; Vraa-Jensen; Wagner et al.). The largest was probably the case described by Vraa-Jensen (fig. 104) in which a male infant of 38 weeks of gestational age, and birth weight of 5525 g., had intracranial contents weighing 2100 g., almost entirely accounted for by tumor tissue. In some of these cases remnants of

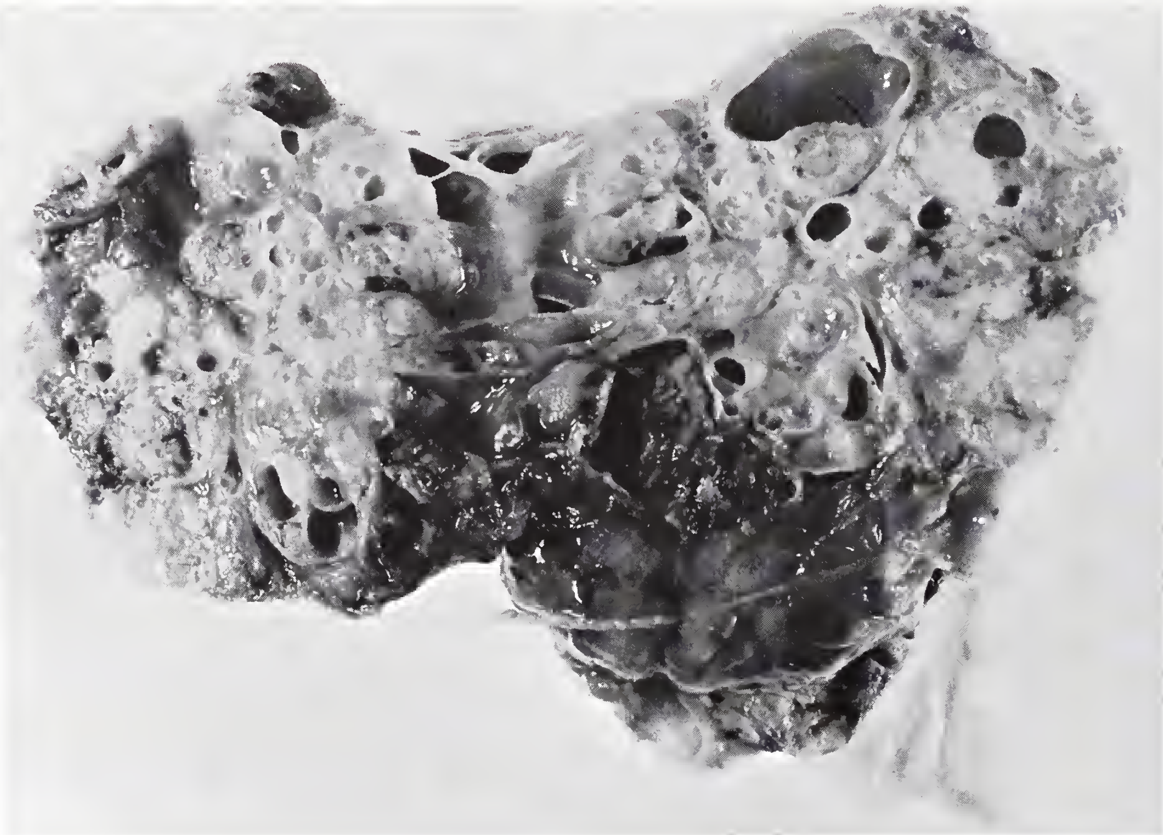
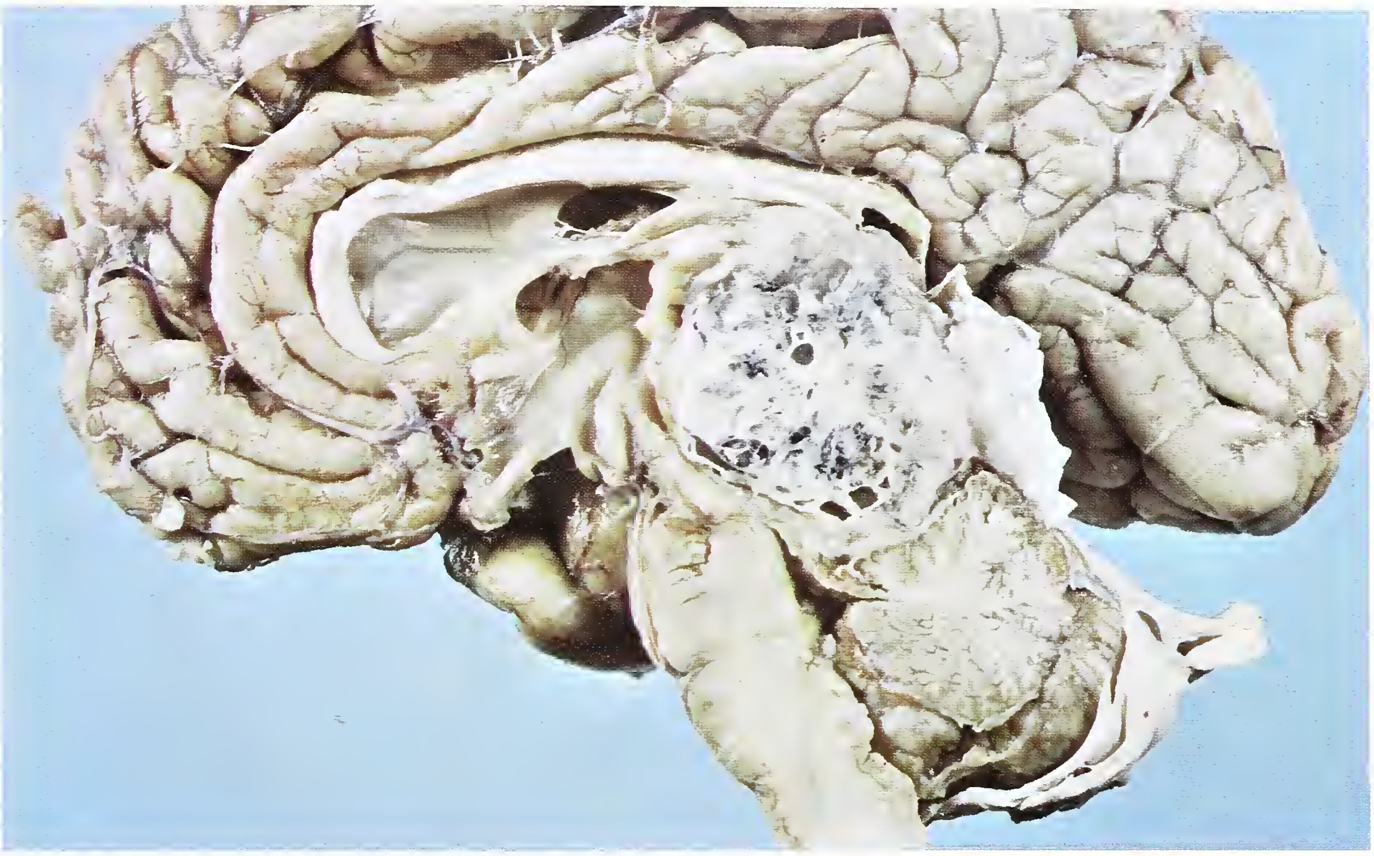
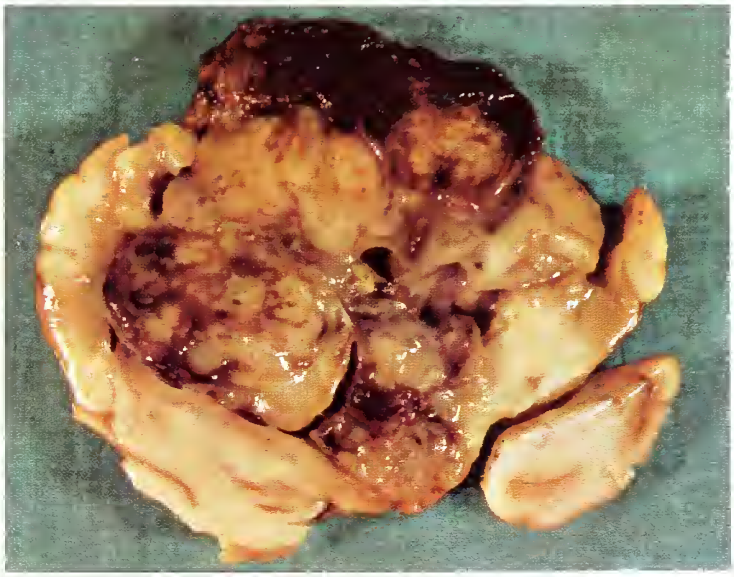


Figure 103
(Figures 103, 107, 108, and 111 from same case)
INTRACRANIAL TERATOMA
Massive congenital intracranial teratoma. (Courtesy of Dr. Lucy B. Rorke, Philadelphia, PA. From Hirsch, L. F., Rorke, L. B. and Schmidek, H. H. Unusual cause of relapsing hydrocephalus. Congenital intracranial teratoma. Arch. Neurol. 34:505-507, 1977.)

PLATE VI
INTRACRANIAL TERATOMA

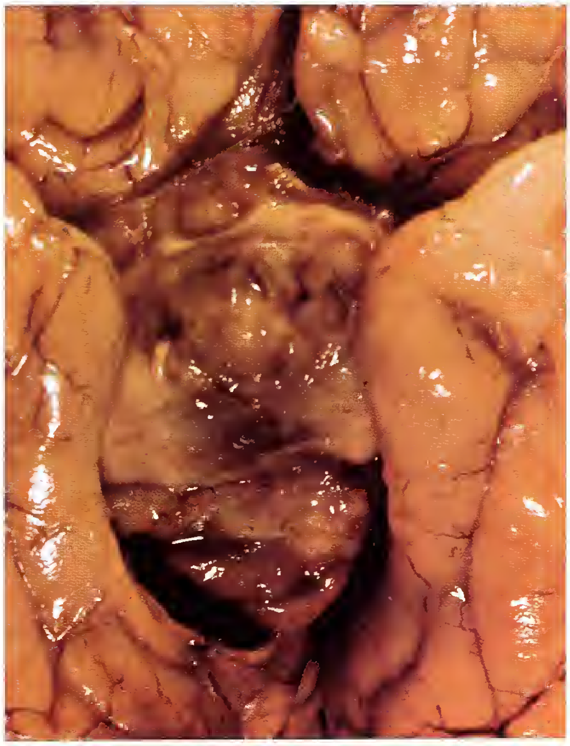


A. Malignant teratoma with a germinoma component. The tumor has grown to distort the mesencephalon and encroach upon the third ventricle. (Courtesy of Dr. Jans Muller, Indianapolis, IN.)



(Plate VI B-C and figure 109 from same case)

B. Coronal section of the brain of a 35 week gestation premature infant who succumbed to a massive intracranial teratoma on the fifth postnatal week. Arising from a midline location, the tumor has obliterated the third ventricle and both lateral ventricles.



C. Ventral view of the floor of the third ventricle in congenital intracranial teratoma. The tumor protrudes as a well circumscribed mass that distends and largely effaces the optic chiasm.

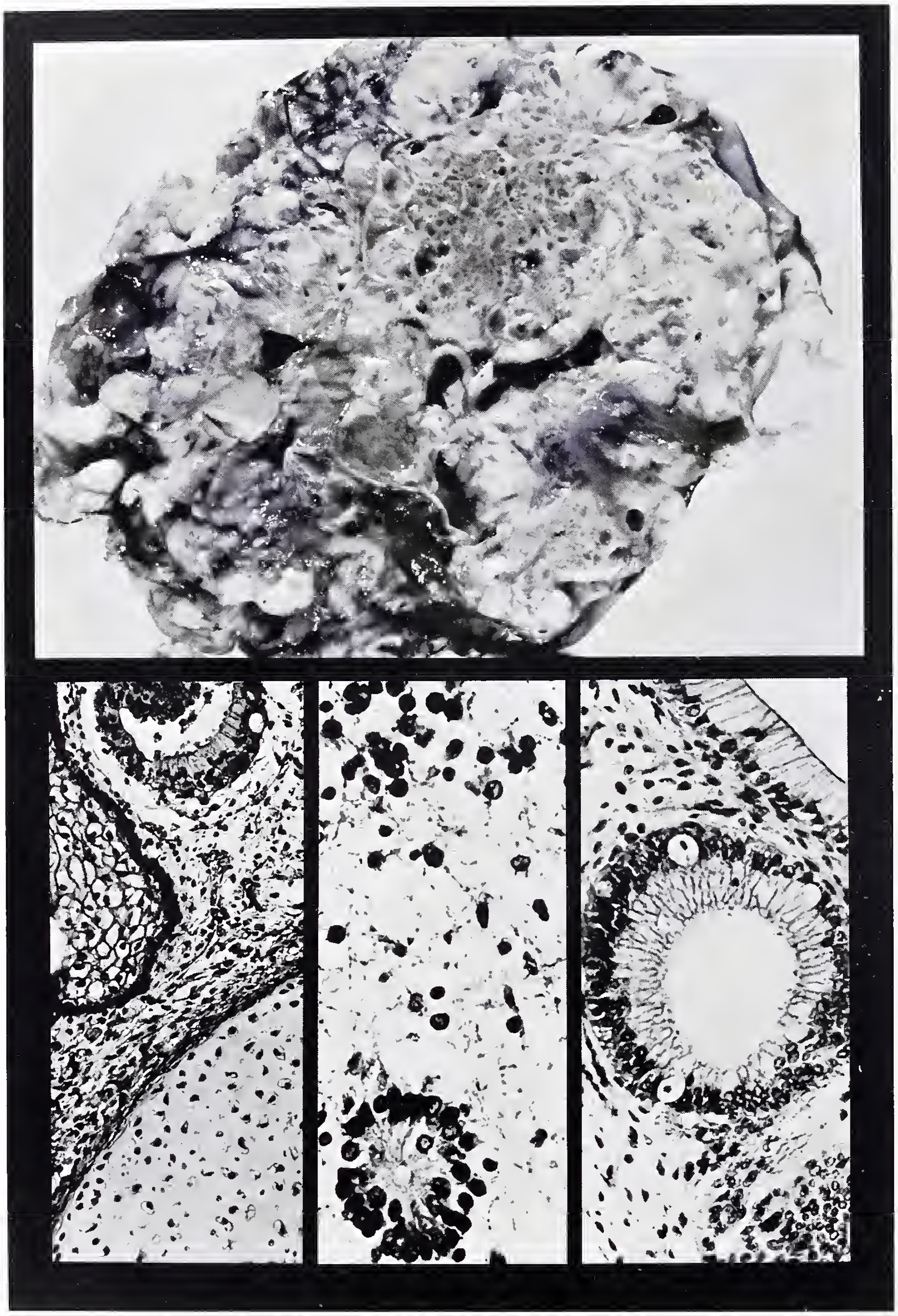


Figure 104
(Figures 104 and 110 from same case)
INTRACRANIAL TERATOMA

Massive congenital intracranial teratoma in which only remnants of brain tissue could be identified microscopically, and the tumor weighed over 2 kg. In the lower half of the illustration are shown some of the different histologic components present in the tumor mass. Left: Squamous epithelium and cartilage, X120; center: immature neuroectodermal cells in rosette formation, X300; right: mucus-producing glands, X165. (Courtesy of Drs. J. Vraa-Jensen and L. Rubinstein, Stanford, CA. From Vraa-Jensen, J. Massive congenital intracranial teratoma. Acta Neuropathol. [Berl.] 30:271-276, 1976.)

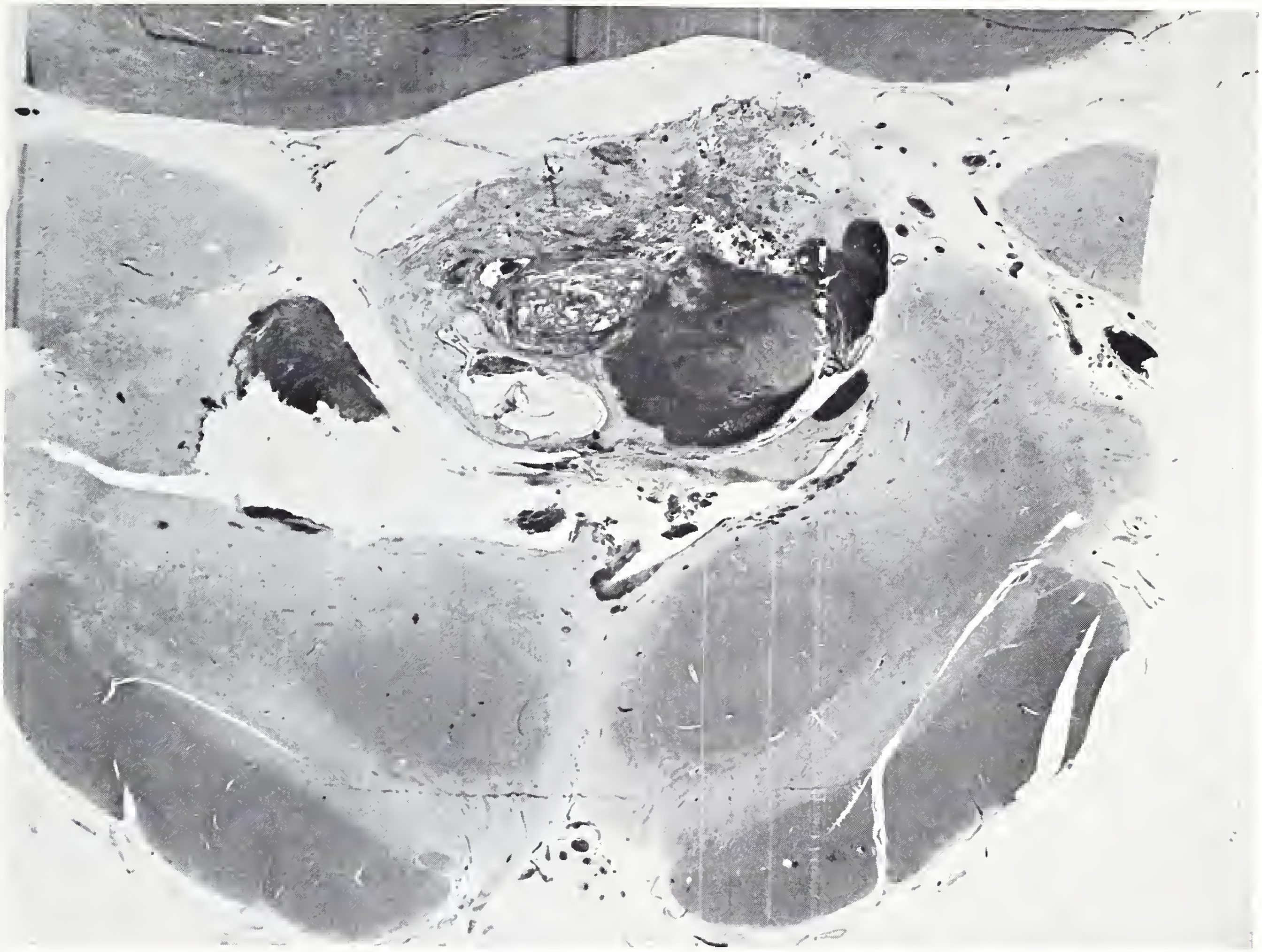


Figure 105
INTRACRANIAL TERATOMA
Malignant teratoma filling the superior cistern and severely compressing the tecum mesencephali. X10. (Courtesy of Dr. Jans Muller, Indianapolis, IN.)

brain substance may be identified only by microscopic examination. In spite of the insistence on the cystic nature of these tumors, Morelli described a teratoma of the fourth ventricle, in a 2 year old girl, that appeared quite solid. The tumor was well encapsulated, and could be entirely removed, but there was a fatal recurrence within three months. Rubinstein separates teratomas of the fourth ventricle as a special category, because of the potential confusion that might arise between teratomas of this region and other primitive tumors of the area, notably medulloblastomas. He has further called attention to atypical microscopic variants, such as medulloblastomas with rhabdomyogenic elements and pigmented papillary neoplasms, tumors whose nosologic definition and possible relationship with teratomas is incompletely elucidated.

If the tumor is predominantly a germinoma, it tends to appear as a poorly circumscribed, light-gray, granular, solid neoplasm. Cystic areas are usually not present. Hemorrhage, necrosis, and degeneration may be seen, but are not common. By the same token, calcification may be large enough to be detected on skull roentgenograms, but is not found in the majority of specimens. When the tumor arises in the posterior part of the third ventricle, the pineal is usually destroyed. The tumor may spread through the ventricular system and seed into the subarachnoid space. Those arising in the anterior third ventricle may extend downward to the infundibulum, optic nerves, and pituitary (fig. 105).

Microscopic Appearance. The malignant intracranial germinomas faithfully reproduce the histologic patterns of gonadal germ cell tumors. Close attention will be given here only to the more recently recognized patterns, or to those aspects of the histologic appearance summarily treated elsewhere.

The microscopic appearance of the usual type of germinoma of the pineal and parapineal areas is identical to the gonadal germinoma (i.e., testicular seminoma or ovarian dysgerminoma). The tumor cells are large, spherical or polyhedral, with sharply defined plasmalemma and pale-staining cytoplasm. Nuclei are vesicular and nucleoli fairly conspicuous (fig. 106); Rubinstein notes that there is no possibility of confusion with primitive cells of the glial series or cells indigenous to the normal pineal gland, since the tumor cells react negatively with silver stains. The characterization of germinoma cells has been extended to the ultrastructural realm, and found to be basically the same in gonadal and pineal germinomas (Pierce; Rubinstein). In addition to the basic neoplastic cell, a lymphocytic stromal component is a regular accompanying microscopic feature of germinomas, regardless of their primary location. Granulomatous reaction in the stroma is also commonly seen. These phenomena are so consistently associated with germinomas as to suggest a unique form of immune response (Marshall and Dayan) of the host tissues to the advancing tumor.

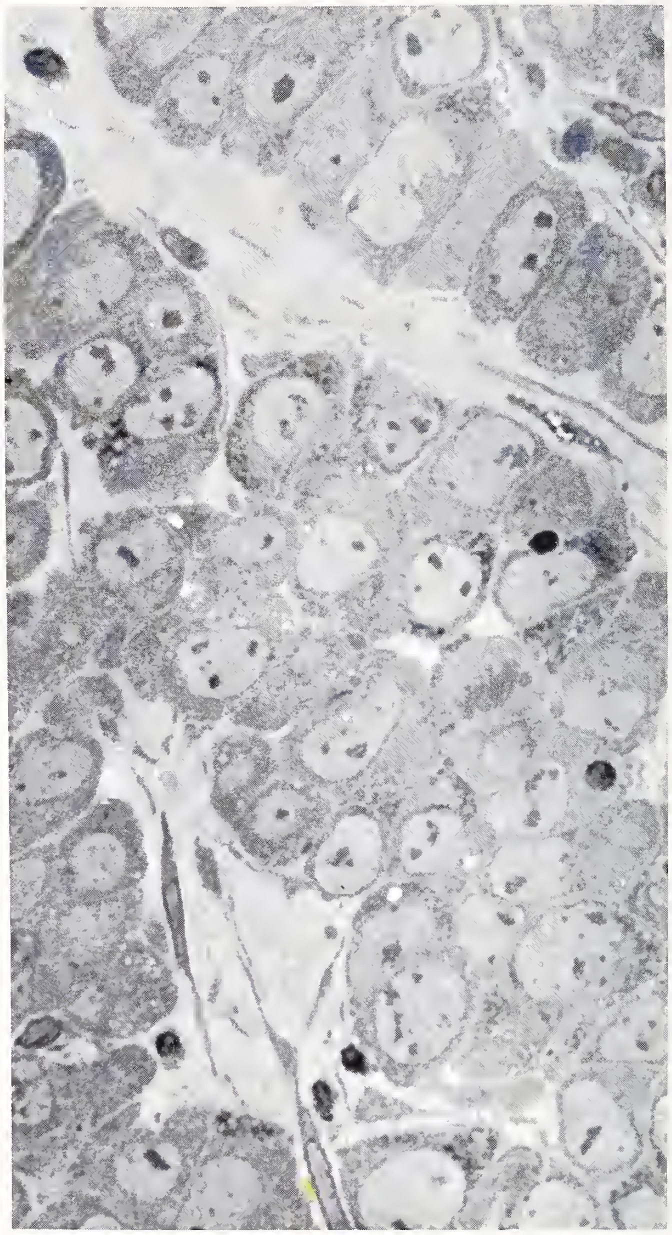


Figure 106
INTRACRANIAL TERATOMA
The cytologic features of this primary pineal tumor appear indistinguishable from testicular seminoma or ovarian dysgerminoma. Pineal germinoma is thus the most appropriate designation. X475.

Most intracranial tumors having the microscopic pattern of choriocarcinoma have occurred in males (Bruton et al.; Glass and Culbertson; Greenhouse and Neuberger; Hutchinson et al.; Stowell et al.), but some are reported in females (Fruhling et al.; Hirano et al.; Musiani and Mancuso).

Syncytial and cytotrophoblastic elements have been regularly identified in these tumors. Tumors associated with high levels of urinary chorionic gonadotropic hormone have been present without evidence of precocious puberty (Hirano et al.). Histologically, tumors with such an endocrine output may show combinations of well differentiated teratoma, embryonal carcinoma, and choriocarcinoma.

The endodermal sinus tumor (synonym: yolk sac carcinoma) constitutes a morphologic type of germ cell tumor that may occur intracranially. The histologic appearance is quite variable, and several of its aspects with diagnostic value have been illustrated in preceding sections (see Sacrococcygeal Teratomas; Mediastinal Teratomas). These may include: formation of loose networks of interanastomosing, flat "mesothelioid" cells set in a myxoid background; presence of so-called Schiller-Duval bodies, consisting of central vessels covered by a peripheral epithelial mantle; primitive cells, either in dense aggregation, or forming cavities and channels, and lying in a myxoid stroma, presumably representing extraembryonic mesoblast; "honeycomb" pattern of microcysts. Of equal diagnostic value is the presence of hyaline material appearing as intracellular rounded globules, or extracellular linear deposits. This material, known to contain alpha-fetoprotein and other embryo specific products, is presumably synthesized by the tumor cells and subsequently extruded to the extracellular space. In ordinary histologic preparations it appears as a PAS positive, diastase resistant substance; immunofluorescent methods may localize the presence of alpha-fetoprotein in this substance. Eberts and Ransburg reviewed the literature and found 17 reported cases of primary intracranial endodermal sinus tumors, 5 of which showed a "pure" histologic pattern. All occurred in the first two decades of life; 14 were pineal or parapineal; 3 were intrasellar or suprasellar; 10 (70 percent) were seen in male patients. From the reviews of Albrechtsen and associates and others (Bestle; Borit), it appears that intracranial yolk sac carcinoma (endodermal sinus tumor) constitutes only about 0.1 percent of all brain tumors, but up to 10 percent of those situated in the midline, especially around the pineal and hypothalamic regions.

The typical teratomas, whether they occur in isolated form or in partnership with germinomas, are characterized by a multiplicity of tissue derivatives, representing the three germ layers (pl. VI-B, C; figs. 107–109). Teratomas of the central nervous system are structurally comparable to teratomas occurring elsewhere. Nervous tissues of one kind or another are among the most common types of tissue found in teratomas (Wagner et al.; Willis, 1971); teratomas originating within the nervous system are an adequate example of this general rule. Tissues in different stages of differentiation may be recognized in these teratomas, from ependymal mantle and fetal tissue resembling myelospongium, to highly organized glial or cortical brain tissue. Neuroepithelial plaques or tubules resembling the neural tube of early embryos appear constituted by dark, densely clustered, tall cells, often with a ciliated luminal border. These structures have been confused with "endometrial glands" (Gerstley et al.) or other glands, a mistake explained by the somewhat glandular appearance of neurotubules. There have been at least two instances of rhabdomyosarcoma arising within a pineal teratoma and becoming the predominant tumor component (Glass and Culbertson; Preissig

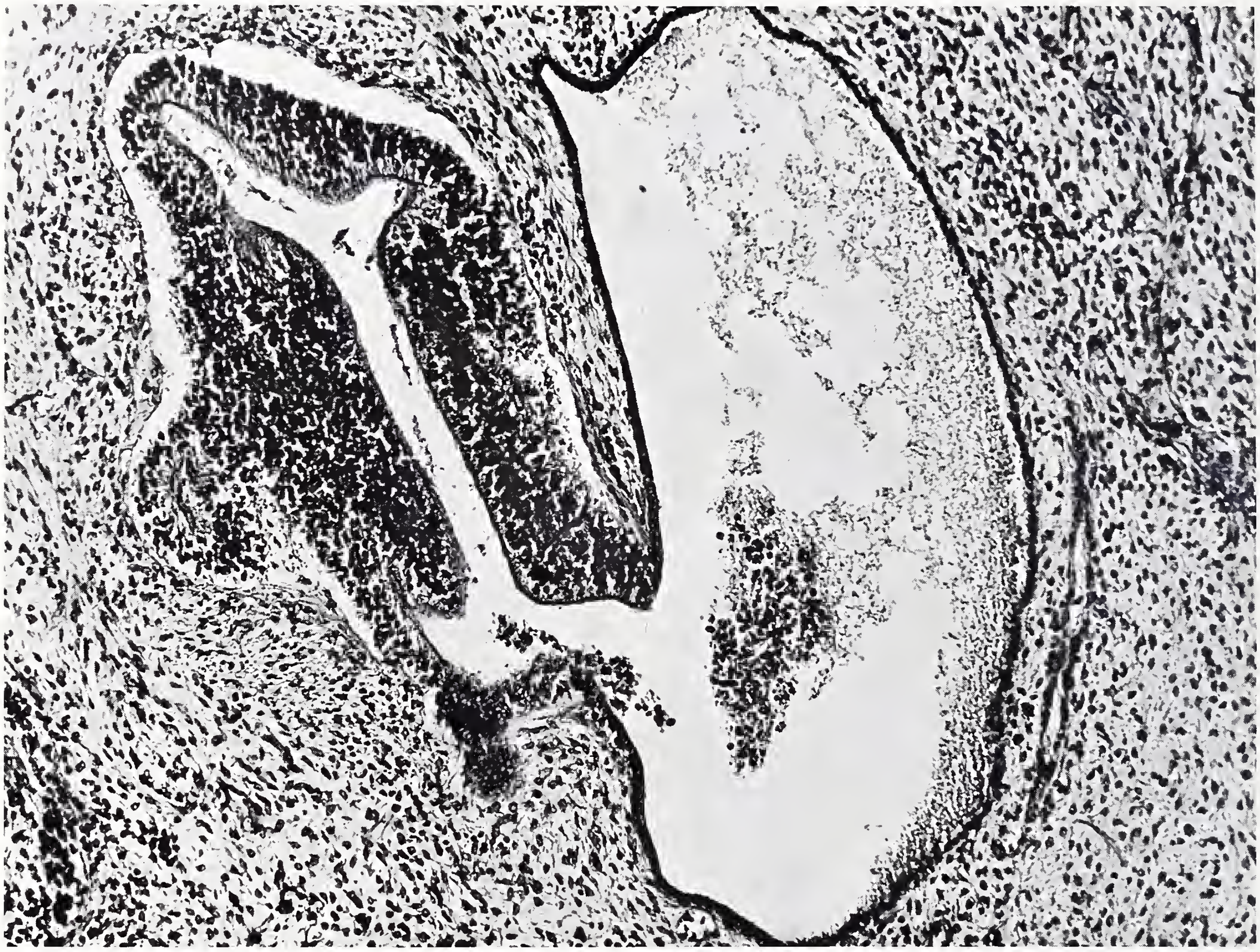


Figure 107
INTRACRANIAL TERATOMA
A cystic structure from the case illustrated in figure 103, partly lined by primitive neural epithelium. X175. (Courtesy of Dr. Lucy B. Rorke, Philadelphia, PA.)

et al.). In one instance, the response to postoperative radiotherapy was poor and the tumor proved fatal to the patient; the other patient died in the immediate postoperative period.

Immature nervous tissue or immature somatic tissues such as testicle (Hirsch et al.), cartilage (Vraa-Jensen), and mucus-producing glands (Greenhouse and Neubuerger) are illustrated in case reports of the uncommon form of neonatal intracranial teratoma (figs. 109, 110). Since most of these patients have died soon after birth, it has been impossible to determine the biologic behavior of these tissues. On the other hand, the presence of abundant amounts of immature tissue in the tumors of these patients, who are young infants, should not be taken as an indication of malignancy. The tissues in question may be expected to mature in the course of time. In his thorough review of the occurrence of nervous tissue in teratomas, Willis noted that senile and degenerative changes, similar to those of the aging brain, are sometimes seen in the nervous system of old, benign teratomas, the most common being the formation of calcospherites or "brain sand." On the other hand, the immature somatic tissues may have the poten-

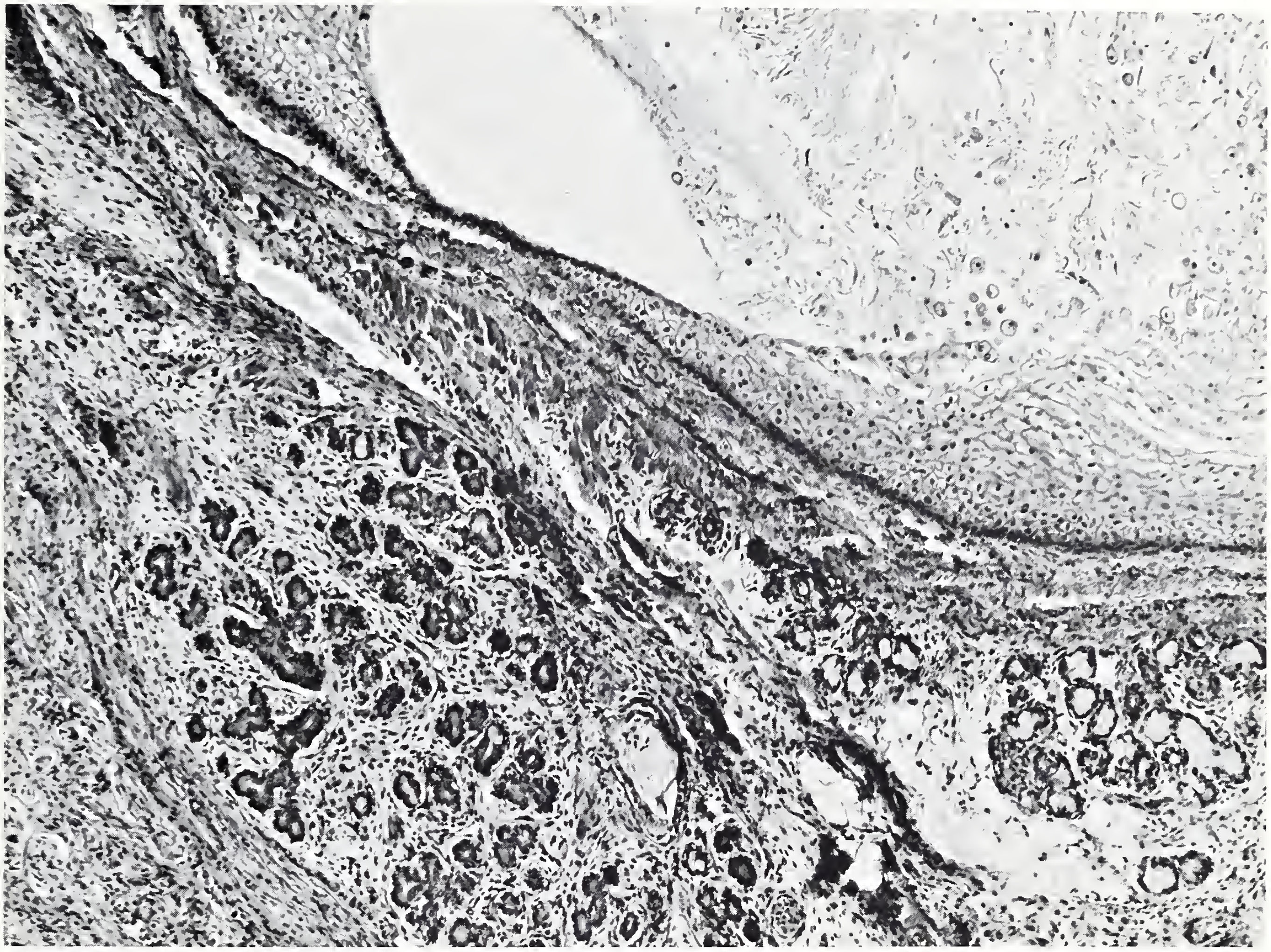


Figure 108
INTRACRANIAL TERATOMA
Diversity of tissue composition of the congenital intracranial teratoma. Present in this field are pancreas, colonic glands, and keratinizing squamous epithelium. X115. (Courtesy of Dr. Lucy B. Rorke, Philadelphia, PA.)

tial for metastatic spread. Willis has reviewed the occurrence of nervous tissue in the metastases of malignant teratomas. It appears likely that this component is also capable of metastasizing via the cerebrospinal fluid. Claims that typical intracranial trigerminal teratomas are invariably benign do not seem warranted (Arseni et al.).

Differential Diagnosis. Clinically, the major consideration is to establish whether the patient has evidence of a neoplasm in the pineal region, and whether hypothalamic signs precede the onset of suprasellar infundibular involvement. The symptoms of hormonal imbalance in suprasellar germinomas are due to direct involvement of the pituitary gland, as well as to infiltration and pressure in the hypothalamus. Clinically, other conditions that involve this general area must be ruled out. These include astrocytomas of the anterior portion of the floor of the third ventricle, arachnoiditis of the optic chiasma, meningioma of the tuberculum sellae, optic nerve glioma, Schüller-Christian disease, and metastatic tumors (Camins and Mount). Of 57 histologically verified tumors of the pineal and suprasellar region reported by the Children's Cancer Study Group in 1979, 36 were germinomas, 7 teratomas, 7 pineal

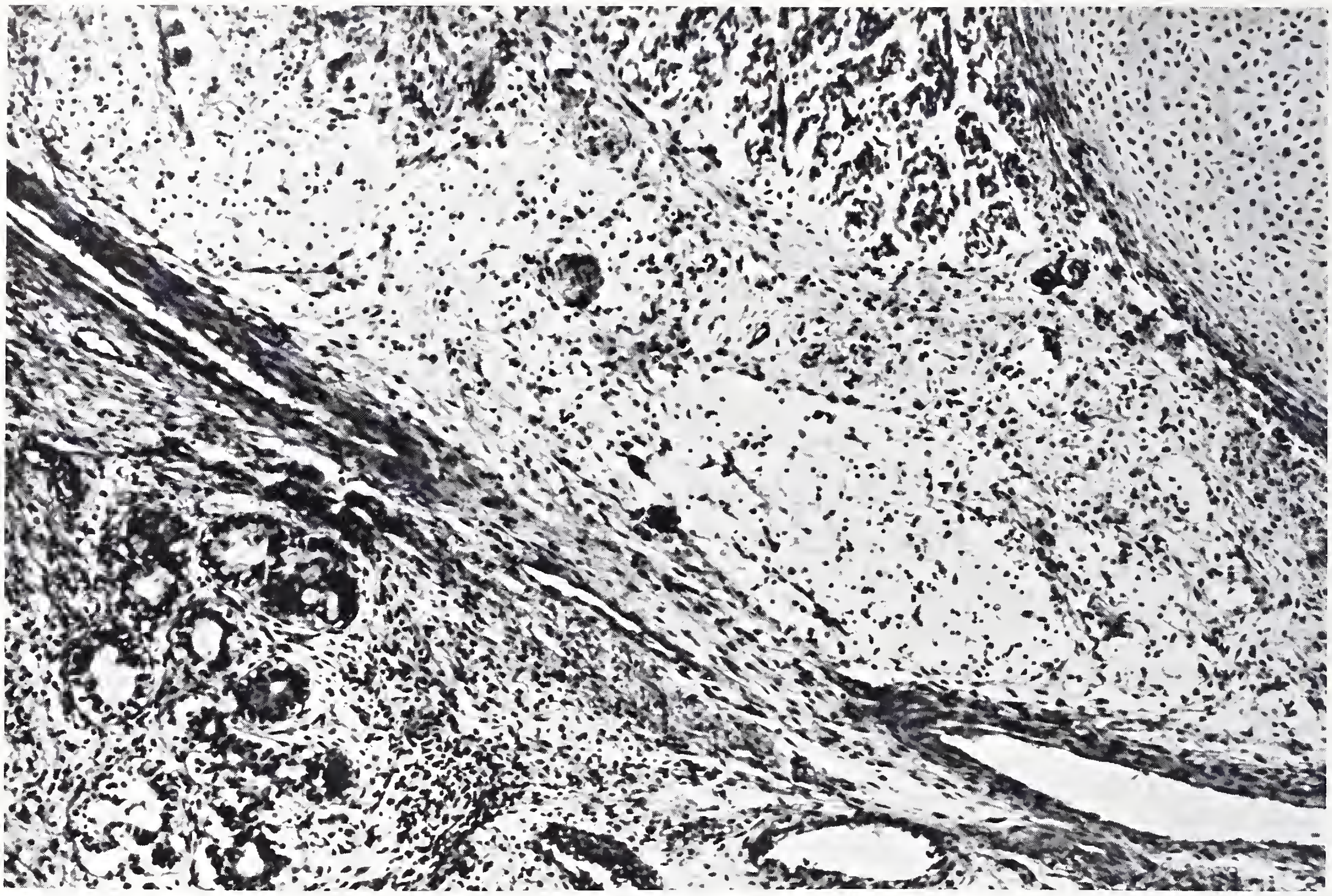


Figure 109
(Figure 109 and plate VI-B and C from same case)
INTRACRANIAL TERATOMA
Heterogeneity of tissues composing the intracranial teratoma illustrated in plate VI (B and C) include: muscle and cartilage (upper right corner), loose fibroadipose tissue (center), and endodermal, mucin-producing glands (lower left corner). X80.

parenchymal tumors, and 2 embryonal tumors; other neoplastic categories were represented by single examples (Wara et al.).

One major difficulty in the differential diagnosis arises when a germinoma is found in the pineal gland, and another tumor in the anterior part of the third ventricle. This can be due to metastasis via the optic pathways, or growth in direct continuity; still other tumors are believed to arise in this anterior part of the third ventricle and metastasize from there (Kageyama and Belsky). The question of multicentricity may be impossible to solve. Camins and Takeuchi have emphasized the difficulty in making an early accurate diagnosis, and stressed the need to pay particular attention to the anterior and posterior third ventricular components of such tumors. Cord metastases are estimated to occur in approximately 10 percent of the cases (Wara et al.). It should be noted that although tumors thus metastasizing most commonly show the structure of germinoma, quite typical (trigerminal) teratomas are also capable of metastasizing, however rarely, via intracerebral pathways. Thus, Hübner described what was considered the third case of a malignant teratoma containing tissues of all three germ layers, which developed extensively upstream and downstream metastases along the cerebrospinal

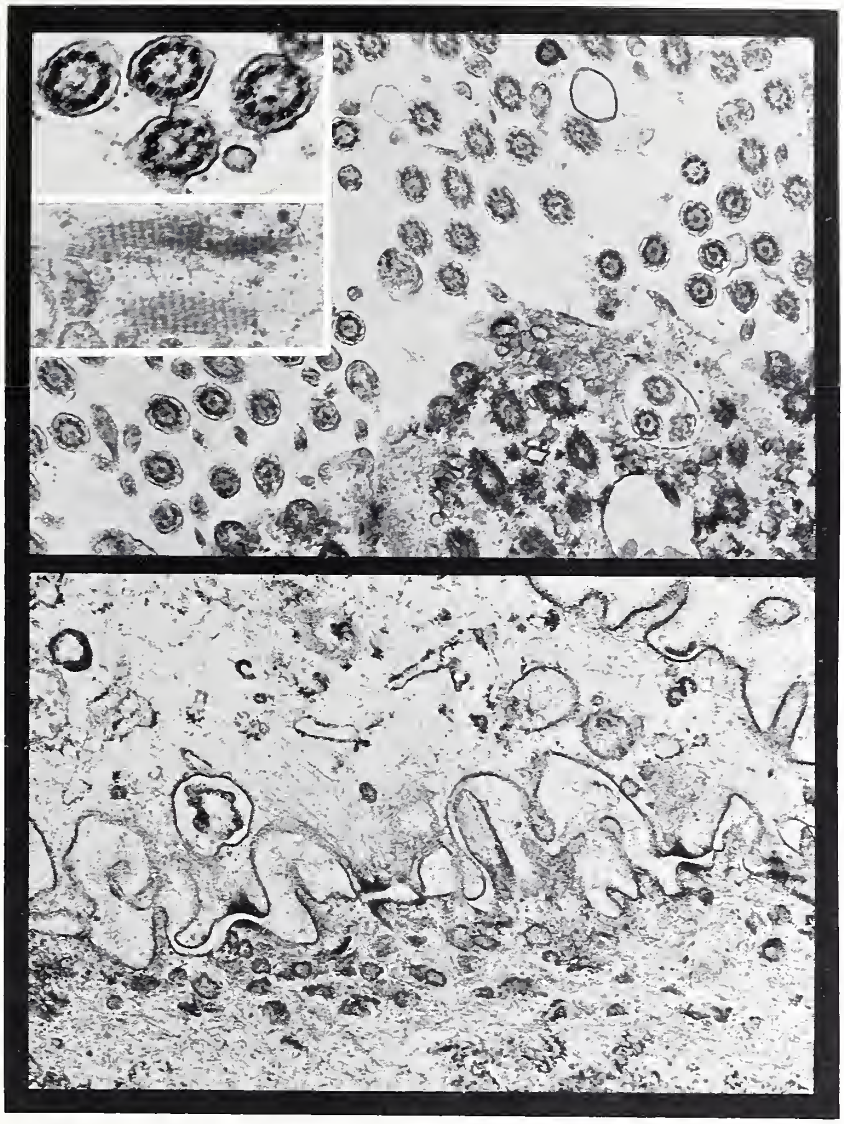


Figure 110
INTRACRANIAL TERATOMA
Ultrastructural study of case illustrated in figure 104 showed ciliated cells with basal bodies (X14,000); details of the cilia and two ciliary rootlets are shown (X30,000). Typical squamous cells with interdigitations and formation of desmosomes are also illustrated (X12,000). (Courtesy of Drs. J. Vraa-Jensen and L. Rubinstein, Stanford, CA. From Vraa-Jensen, J. Massive congenital intracranial teratoma. Acta Neuropathol. [Berl.] 30:271-276, 1976.)

flow pathway. In a more recent case, reported by Hirsch and associates, an epidermal, keratinized cyst with a few glandular structures was present in the thoracic spinal subarachnoid space of a female infant who died with a large intracranial teratoma. The latter authors raised the questions that epitomize the dilemma of differential diagnosis in such cases: whether the two lesions represent multicentric origin, or one primary and one metastasis, or whether one is a teratoma and the other a malformative cyst. It is unlikely that these questions may be settled by purely morphologic means. Although teratomas may associate with malformations, the finding of a well differentiated cystic structure in the subarachnoid space of a patient with a large intracranial teratoma may be reasonably considered to be a "drop" metastasis (fig. 111). The alternative possible diagnosis is "epidermoid cyst," a benign slow-growing lesion which is sometimes seen in intracranial location. This lesion very likely represents a malformation of displaced squamous epithelium that becomes included within the embryonic body early in morphogenesis. Intracranial epidermoid cysts occur preferentially at the cerebellopontile angle, less commonly in

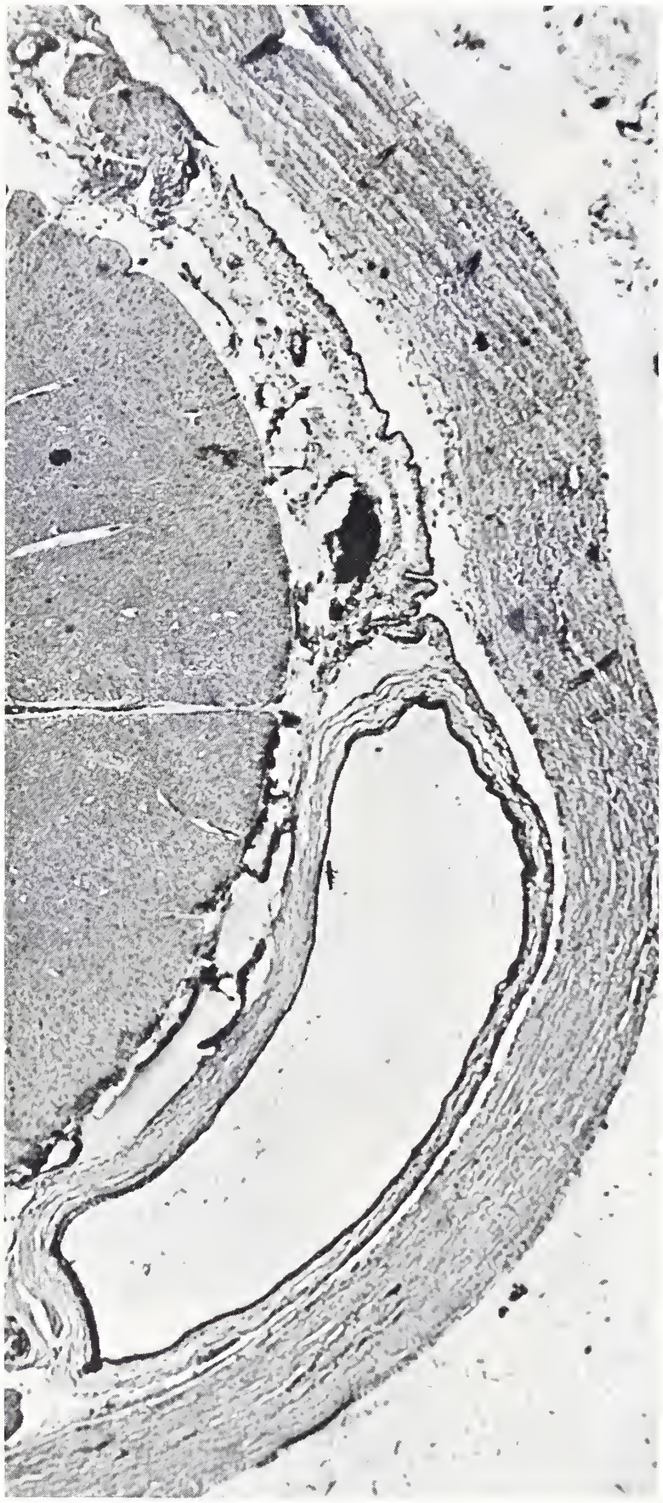


Figure 111
INTRACRANIAL TERATOMA

Spinal subarachnoid cyst lined by mature cuboidal epithelium, found at autopsy in the patient with the massive congenital intracranial teratoma shown in figure 103. X10. (Courtesy of Dr. Lucy B. Rorke, Philadelphia, PA. From Hirsch, L. F., Rorke, L.B., and Schmidek, H. H. Unusual cause of relapsing hydrocephalus. Congenital intracranial teratoma. Arch. Neurol. 34:505-507, 1977.)

other locations; three cases have occurred in the brainstem (Weaver and Coulon). On occasion, an intracranial epidermoid cyst undergoes malignant transformation into squamous carcinoma: thirteen such cases have been reported, including one in a 4 year old child (Nosaka et al.). In the presence of malignant squamous epithelial tissue within the skull, it becomes imperative to rule out an extracranial epidermoid carcinoma as the potential source of intracranial metastases. Concerning other tumors of germ cell origin, whether seminoma, embryonal carcinoma, endodermal sinus tumor, or choriocarcinoma, a diagnosis of primary intracranial origin cannot be accepted unless the gonads are excluded as the primary site of the tumor by thorough investigation.

One important pitfall applicable to the microscopic differential diagnosis of germinoma refers to its distinction from other pathologic infiltrates of uniform, small, round cells. As Rubinstein points out, lymphoreticular tumors and leukemic proliferations may selectively involve the neurohypophysis and the hypothalamus.

Prognosis. The congenital form of intracranial teratoma has a very poor prognosis. However, Greenhouse and Neubuerger called attention to the occasional possibility of surgical removal, particularly in those cases of children who appear normal at birth and experience rapid expansion of the cranium in the early weeks of life. Their prediction has been validated by subsequent experience, although long-term survivors after neurosurgical removal still remain exceptional (Takaku et al.), largely because of the size of these tumors at the time of birth. The high morbidity and mortality that attends operative efforts to remove germ cell tumors of the pineal and parapineal areas is due to the tumor's proximity to vital structures. For this reason, the surgical management is often confined to the creation of shunts for the relief of increased cerebrospinal fluid pressure, followed by radiotherapy. With this approach, figures as high as 60 percent five-year, disease-free survivals have been reported (Cummins et al.; Sheline). The Children's Cancer Study Group (Wara et al.) reported an overall survival rate of 66 percent for all tumors of the pineal and suprasellar region treated primarily by radiotherapy.

Treatment. Intracranial germinomas are highly radiosensitive tumors. Whereas no five-year survivors were noted in the review undertaken in the sixties by Rubin and Kramer when these tumors were treated only by removal, Sheline reported 57 percent survival of histologically confirmed germinoma cases treated with radiotherapy. Thus, current treatment of germinomas relies largely on radiotherapy. There are, however, several problems connected with analysis of the results of treatment in this disease. The intraoperative mortality for either resection or biopsy alone, reaches 34 percent (Rubin and Kramer). Many cases, therefore, are treated without previous biopsy. Hence, it is difficult to be sure of the effect of this therapy on pineal and parapineal tumors of different histology. It is reasonable to assume that this effect would tend to be less pronounced on mature, well differentiated somatic tissues than on primitive germ cells. Direct surgical exploration is reserved for patients in whom preoperative work-up has shown a high likelihood of benign tumor. Similarly, if a patient has already undergone a full course of radiotherapy and a shunting procedure, and after some time shows signs of tumor progression, it may be advisable to take the risk of an operative procedure as the best chance of survival. Under such circumstances a new course of radiotherapy may provoke extensive brain necrosis. It is also stated that the lesion would have a greater chance of being benign than in an otherwise unselected population (Schmidek).

The suprasellar germinomas, in contrast to those of the pineal region, can be safely explored at the time of diagnosis. Schmidek discussed the operative approaches and concluded that there is little justification for blind irradiation of a tumor without surgery when it is suprasellar in location. There remains the question of whether a more aggressive surgical approach might result in a higher spinal seeding rate. In the CCSG study (Wara et al.), 14 percent of biopsy proved germinomas had spinal metastases in contrast with only 1.4 percent of patients without biopsy. This problem is currently under investigation.

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◆

SOME TERATOMAS OF UNCOMMON SITES

TERATOMA OF THE PLACENTA

Joseph and Vogt reviewed the literature on placental teratomas in 1972 and stated that no reports of this condition had appeared in the preceding eight years. The sporadic nature of reports adequately reflects the scarcity of case observations. It is quite possible that some of these growths may be confused with "fetus amorphus," and reported under this or a similar designation. In 1964, Fox and Butler-Manuel reviewed 65 reports of placental growths lacking in tissue organization and previously published under the title of "fetus amorphus." They concluded that five of those should be reclassified as teratomas. The diagnostic criteria are the presence of a central skeleton with recognizable cranial and caudal ends in "fetus amorphus" and the absence of such landmarks in teratomas. The degree of organization in "fetus amorphus" permits recognition of individual bones, such as ribs, pelvis, and base of the skull, whereas bone tissue in placental teratomas has not been organized to a degree permitting individual bone identification. Since "fetus amorphus" is considered to be an acardiac blighted fetus, or rudimentary twin, it follows that it should have its own umbilical cord. Absence of a cord is, therefore, another criterion to distinguish a placental teratoma from this condition.

Clinical Features. Some features of recently reported clinical histories of pregnancies resulting in teratoma-bearing placentas are summarized in Table 4. Only one of the conceptuses had multiple congenital anomalies, but the data appear too scanty to obtain statistically valid conclusions about potential noxious effects on the conceptus.

Gross Appearance. Characteristically, teratomas that occur in the placental membranes or on the chorionic plate are described as covered by wrinkled skin and appearing as polypoid, rounded, or ovoid masses strikingly different from the surrounding glistening membranes. Blood vessels may be seen to penetrate the parenchyma from the surrounding vessels of the placental roof, or from the umbilical cord; however, these vessels are devoid of Wharton's jelly (pl. VII-A; fig. 112).

Teratomas of the umbilical cord may also give the appearance of skin-covered swellings placed at variable distances between the placental and the fetal attachment sites of the cord. The parenchyma is composed of firm and soft tissues with interposed cystic spaces (pl. VII-B, C).

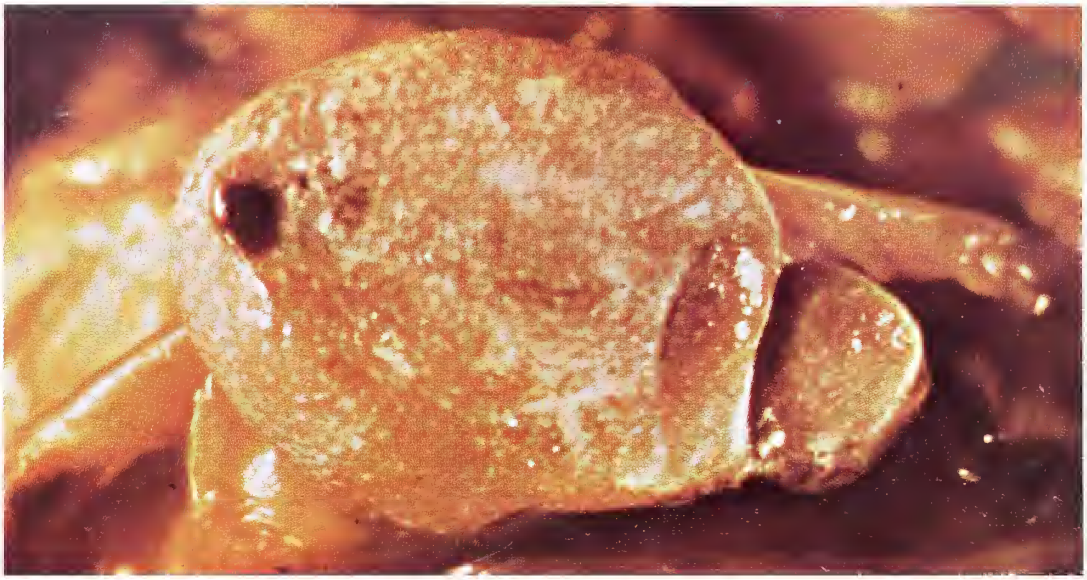
Microscopic Appearance. Polystratified squamous epithelium covers the surface of these masses, thus accounting for the similarity with an abnormal, skin-covered blighted twin. In Joseph and Vogt's case, two vessels joined the tumor to the chorionic plate, 2.0 cm. distant from the mass (pl. VII-A; fig. 112). These vessels had no Wharton's jelly around them and were not considered the equivalent of an umbilical cord. A diagram was prepared by Fujikura and Wellings to show the distribution of tissues in their case. The surface of the teratoma was covered by skin, with its appendages merging at the base of implantation with the fetal membranes. The central core was composed of fatty tissue

Table 4

PLACENTAL TERATOMAS

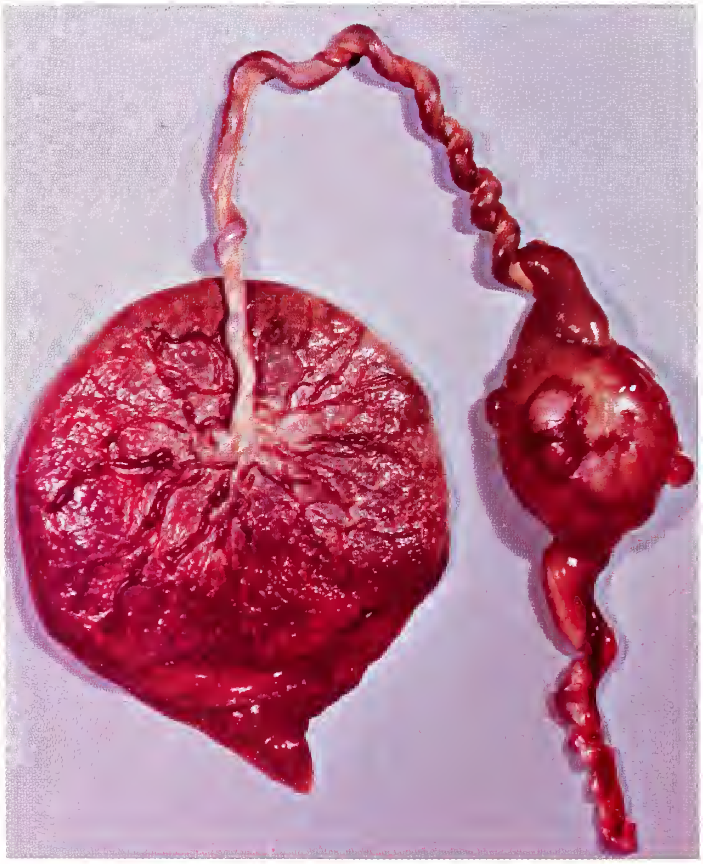
Author	Location of Tumor	Tumor Size	Maternal Age (yrs.)	Tumor Weight	Obstetrical Data	Gestational Age	Birth Weight	Associated Condition
Morville	Membranes of chorionic plate	"nut-sized"	17		GI, PO	full term	3000 g.	
Kreyberg	Umbilical cord	"bulky"	33		GII, PI	35 weeks still birth		Small rupture of cord
Heckmann et al.	Umbilical cord	9 x 7 cm.	32		GIII, PII	full term healthy	3100 g.	
Fox and Butler-Manuel	Membranes between amnion and chorion	7.5 cm.	36	150 g.	GII, AI congenital syphilis	38 weeks	male 3400 g.	Breech, Cesarean section
Fujikura and Wellings	Chorionic plate near cord insert	3 x 1.4 x 1.2 cm.	20		GII, PI, AI		male 3400 g.	Multiple congenital anomalies
Joseph and Vogt	Membranes between amnion and chorion	2 cm.	26		GIII, PI, AI	35 weeks	2126 g.	Eccentric, 30 cm. cord

PLATE VII
PLACENTAL TERATOMA



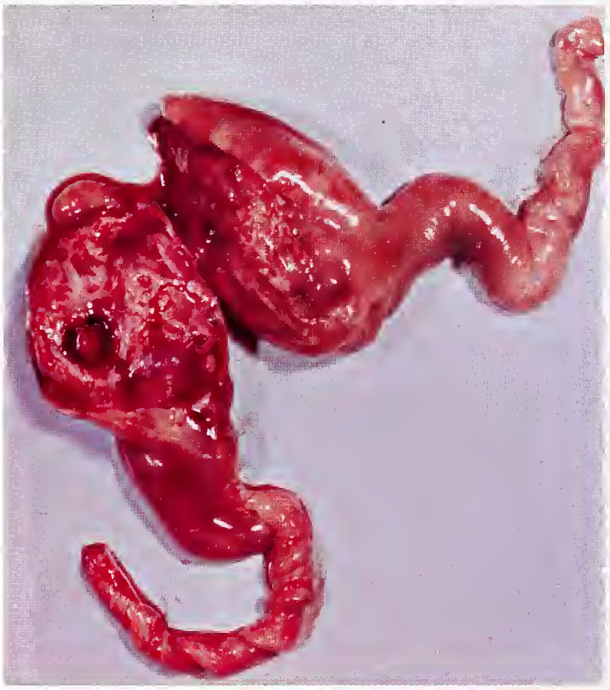
(Plate VII-A and figure 112 from same case)

A. Gross appearance of a teratoma of the placenta originating from fetal membranes. (Courtesy of Dr. P. J. Vogt, Oakland, CA.)



(Plate VII-B and C from same case)

B. Gross appearance of placental teratoma originating in the umbilical cord. (Courtesy of Dr. V. Freudenberg, Kassel, Germany. From Heckmann, U., Cornelius, H. V., and Freudenberg, V. Das Teratom der nabelschnur. Ein kasuistischer Beitrag zu den echten Tumoren der nabelschnur. Geburtshilfe Frauenheilkd. 32:605-607, 1972.)



C. Cut surface of umbilical cord teratoma. (Courtesy of Dr. V. Freudenberg, Kassel, Germany. From Heckmann, U., Cornelius, H. V., and Freudenberg, V. Das Teratom der nabelschnur. Ein kasuistischer Beitrag zu den echten Tumoren der nabelschnur. Geburtshilfe Frauenheilkd. 32:605-607, 1972.)

containing nerves, ganglion cells, colonic glands, and bundles of smooth muscle (fig. 113).

Differential Diagnosis. The main differential diagnosis is with so-called fetus amorphus, or "fetus acardius," which derives its circulation from the co-twin; the conventional criteria have been discussed in the introductory paragraph of this section. Other tumors may arise in the placenta, such as chorioangiomas, or in the umbilical cord, such as fibromyxomas (Fox). The microscopic appearance of teratomas is so highly characteristic, however, that no difficulties in differential diagnosis should arise after histopathologic examination.

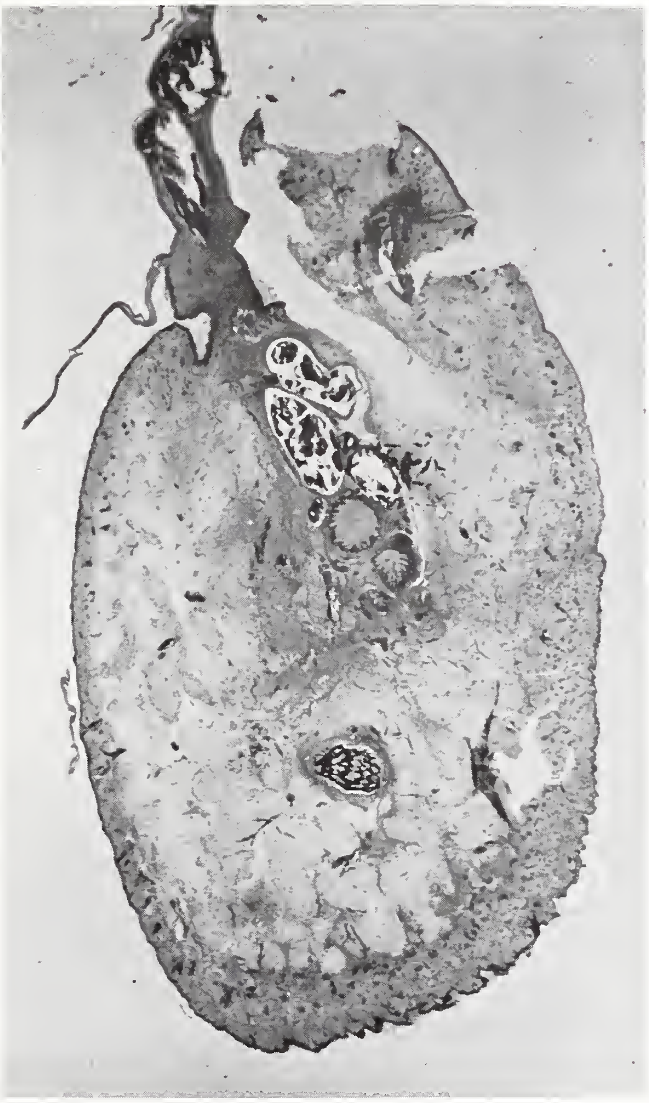


Figure 112
(Figure 112 and plate VII-A from same case)
PLACENTAL TERATOMA
The tumor is polypoid, skin-covered, and the central core contains a variety of tissues: the nodule with dark striae corresponds to bone; cystic spaces are intestinal (endodermal structures). At the base of implantation on the fetal membranes, large vessels are seen (From Joseph, T. J. and Vogt, P. J. Placental teratomas. Obstet. Gynecol. 41:574-578, 1973.)

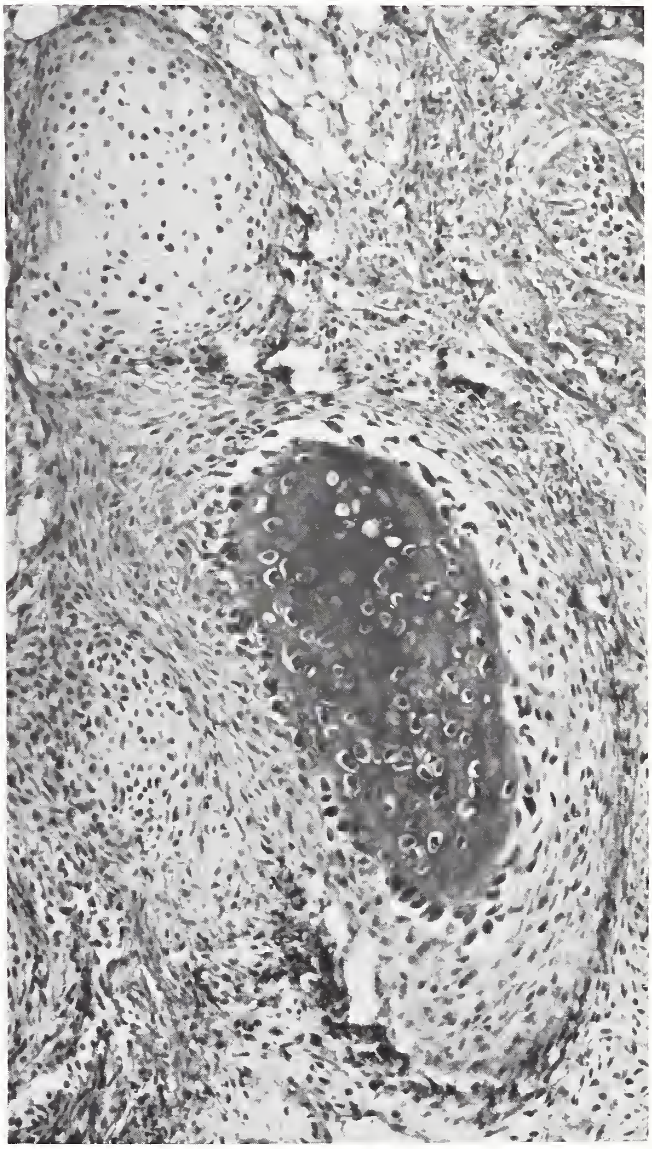


Figure 113
PLACENTAL TERATOMA
Mesenchymal component of umbilical cord teratoma showing foci differentiation into mature bone, cartilage, fibrous and adipose tissue. X275.

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TERATOMA OF THE HEART

Teratomas may develop inside the pericardial sac, where they develop intimate attachments to the root of the great vessels; often they derive their blood supply from adventitial vessels of the aorta, and even from the coronary arteries (Arciniegas et al.). These tumors have been discussed in the section on Intrapericardial Teratomas. However, an endomural origin, i.e., true intracardiac origin, is also possible; we have been able to find five reported instances of such an occurrence, all discovered during postmortem study. Some of their clinical and pathologic features appear summarized in Table 5. Two were benign (Van der Hauwaert; Williams) and three malignant (Arshadi and Watson; Cabañas and Moore; Solomon). Four occurred in children ages 1 day to 4 years. The only adult affected was a 56 year old man; his tumor was clinically and histologically malignant, and metastasized to the skeleton (figs. 114–117).

The tumor described by Williams was a typical benign, multicystic, spheroidal teratoma that arose from the interventricular septum and protruded into the right ventricle, where it showed a mobile projection passing through the pulmonary valve. The illustrations leave no doubt about the nature of this case. Although not illustrated, the other benign tumor was apparently also a typical multicystic teratoma (Van der Hauwaert). Documentation is less complete in the two malignant tumors of children. The 2 year old girl reported by Solomon had a tumor histologically characterized by glandlike structures within a loose, myxomatous matrix; mention was made of cysts lined by columnar ciliated and squamous epithelium. Only glandlike spaces composed the metastases. Apparently, neither neuroectodermal differentiation nor mature mesenchymal structures were seen. The single illustration and the very rapid clinical course suggest the possibility of a highly malignant tumor of germ cell derivation. The same is true of the case reported by Arshadi and Watson under the name of "teratocarcinoma" of the heart. The "trophoblastic" nature of the malignant cells was unconvincingly portrayed. The four tumors classified as malignant cardiac teratoma in the Armed Forces Institute of Pathology collection were described as originating within the pericardial sac and secondarily invading the heart (McAllister and Fenoglio). In one of them a large portion of the tumor grew into the cavity of the right ventricle. Two tumors were characterized by extensive areas of embryonal carcinoma, one had squamous cell carcinoma, and the fourth contained embryonal carcinoma and choriocarcinoma.

Table 5

INTRACARDIAC TERATOMAS

AUTHOR	SEX	AGE	SITE OF ORIGIN	HEART WEIGHT	TUMOR SIZE	METASTASES
Solomon	F	2 yrs.	IAS	2100 g.	not stated	lungs, orbital bones
Van der Hauwaert	M	1 day	IAS and IVS	not stated	"large"	none
Arshadi and Watson	F	4 yrs.	IVS and RV	225 g.	9 x 8 x 8 cm.	lungs
Williams	M	20 days	IVS and RV	60 g.	2 cm. diameter	none
Cabañas and Moore	M	56 yrs.	IVS and RV	300 g.	7 x 3 cm.	thoracic and lumbar vertebrae

Abbreviations: IAS: interatrial septum; IVS: interventricular septum; RV: right ventricle

In adults, most primary intracardiac tumors are myxomas, but in children a wider variety of histopathologic diagnoses may be expected. In infants, more than 75 percent of cardiac tumors and cysts are rhabdomyomas and teratomas (McAllister and Fenoglio). In older children rhabdomyomas predominate, but myxomas approach in frequency teratomas and fibromas. There is practical importance to these diagnostic distinctions because, as Van der Hauwaert points out, teratomas, fibromas, and myxomas are usually amenable to complete surgical resection whereas rhabdomyomas, frequently multicentric, cannot be totally resected.

Clinically, congestive heart failure with obvious cardiomegaly that cannot be explained on the basis of congenital cardiac malformation, fibroelastosis, storage disease, or myocarditis evokes the suspicion of intracardiac tumor. This suspicion is enhanced by the additional discovery of heart murmur associated with rhythm disturbances, peripheral arterial embolization, or atypical features of the murmur, such as change in its character influenced by posture

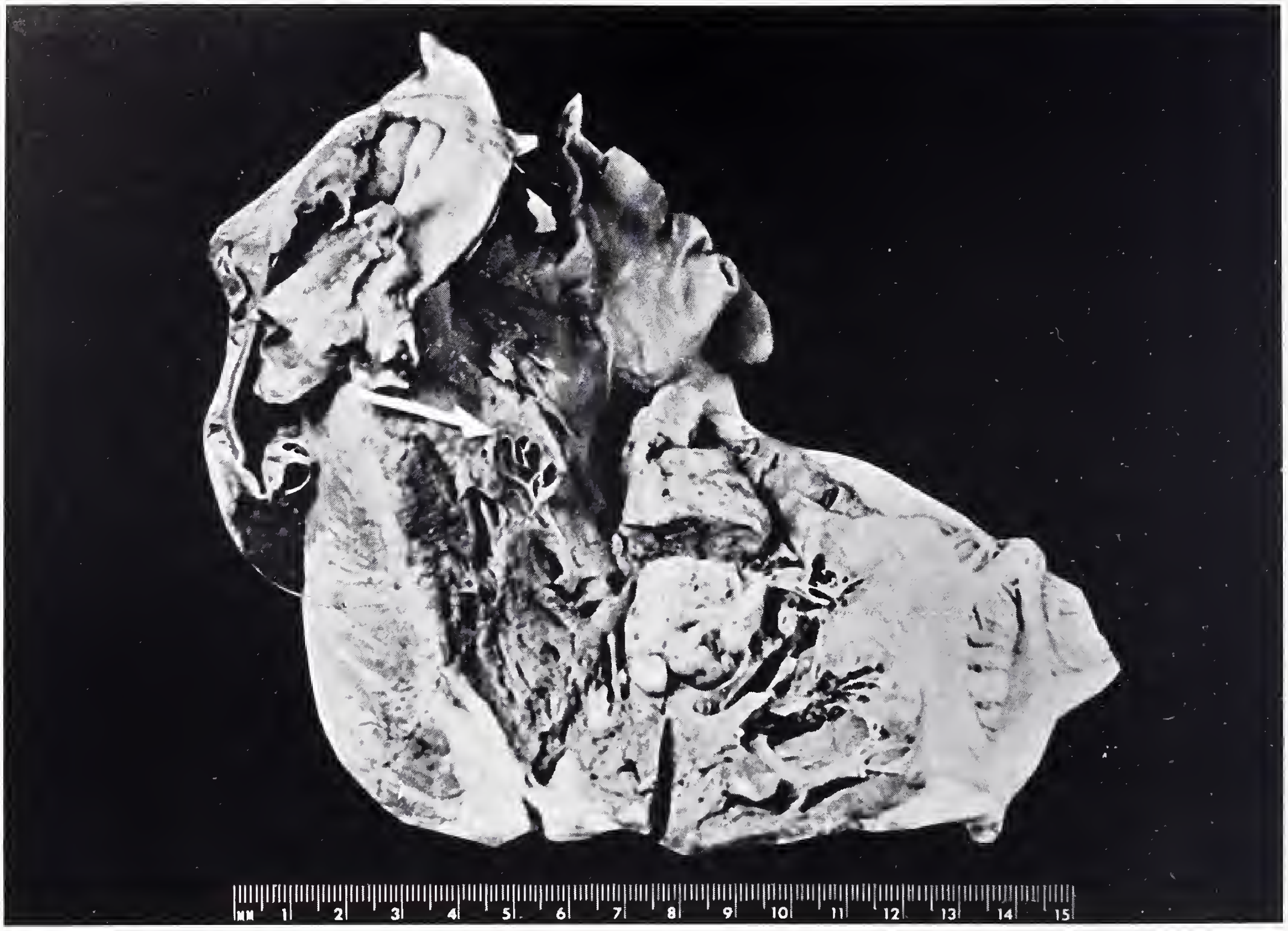

Figure 114
(Figures 114—117 from same case)
CARDIAC TERATOMA

Intracardiac teratoma in an adult. The tumor protrudes into right atrium and right ventricle, on septal side. Arrow points to tricuspid valve. (Courtesy of Dr. V. Y. Cabañas, Cincinnati, OH. From Cabañas, V. Y. and Moore, W. M. Malignant teratoma of the heart. Arch. Pathol. 96:399-402, 1973.)

(Van der Hauwaert). There may also be disproportion between the severe degree of cardiomegaly and the mild valvular dysfunction. Roentgenologic examination may disclose a bulging mass on the cardiac border, and the diagnosis of teratoma is suggested if this mass contains calcific deposits. Ultimately, angiography delineates the anatomic relationships of the tumor. Its use in conjunction with pneumopericardium may be helpful to further define the relative position of the mass. Ultrasound, an ever more widely used noninvasive technic, has proved useful in the preoperative diagnosis of intrapericardial teratoma (Farooki et al.). McAllister and Fenoglio state that since the advent of modern radiologic technics (post 1960), it was possible to accurately establish the extracardiac position of all the intrapericardial teratomas collected at the Armed Forces Institute of Pathology, before surgical intervention.

The histopathologic differential diagnosis of intracardiac teratomas must encompass lesions composed of tissues foreign to the heart. These include cysts

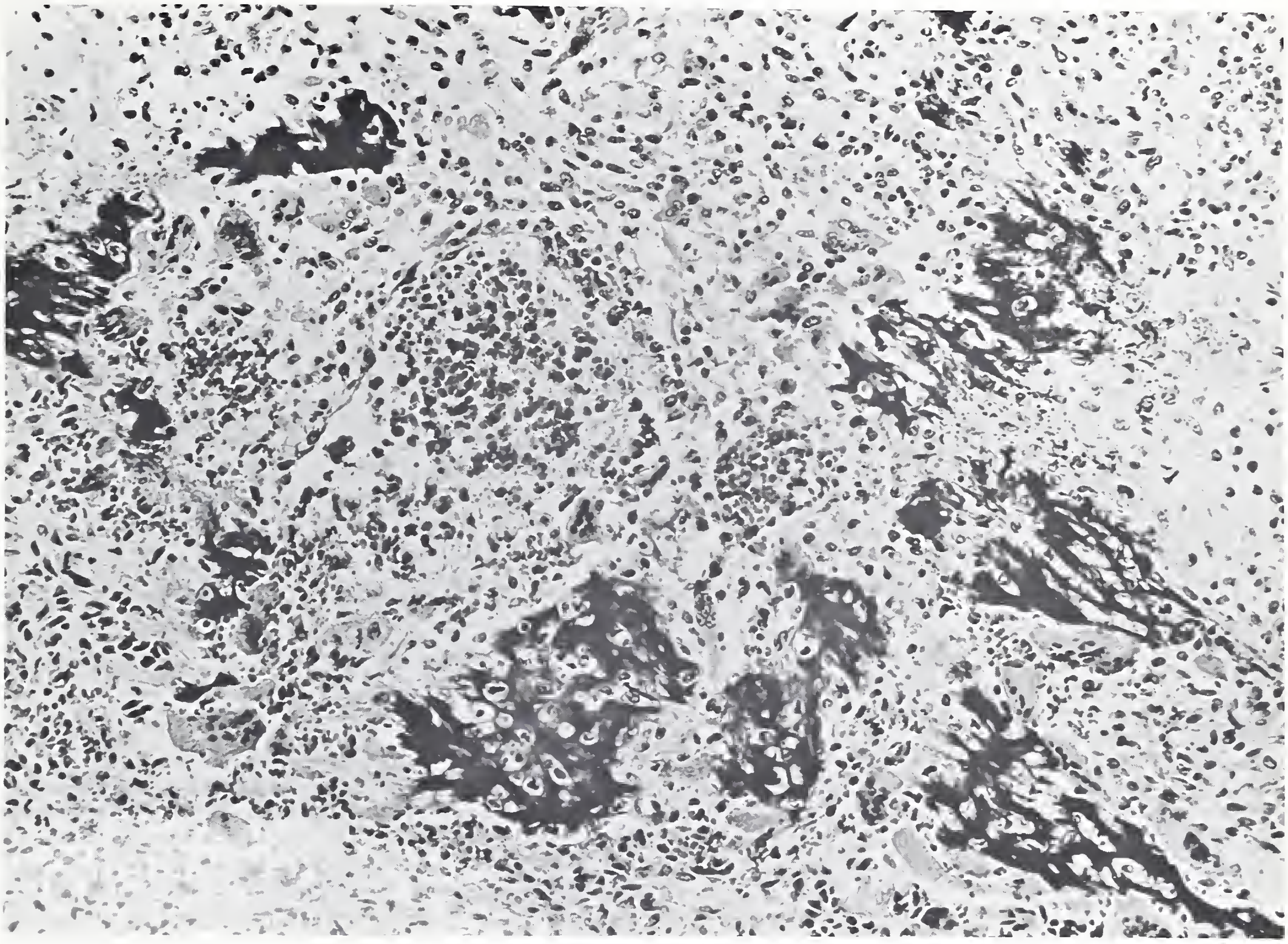

Figure 115
CARDIAC TERATOMA
Foci of ossification and osteoclast-like giant cells. X250. (Courtesy of Dr. V. Y. Cabañas, Cincinnati, OH. From Cabañas, V. Y. and Moore, W. M. Malignant teratoma of the heart. Arch. Pathol. 96:399-402, 1973.)

and heterotopias. Bronchogenic cyst, which is usually extracardiac, may be found deep inside the myocardial substance, sometimes projecting into a cardiac chamber (McAllister and Fenoglio). Unlike teratomas, bronchogenic cysts lack ectodermal derivatives. Heterotopic islands of thymic tissue and thyroid tissue are rarely present in the heart (McAllister and Fenoglio), but are structurally different from teratomas, since they lack the heterogeneous mixture of tissues of the three germ layers that one sees in teratomas. Usually, tissue heterotopias are incidentally discovered as "microscopic rests" in autopsy studies. However, Dosch reported a unique case ("intracardiac accessory thyroid gland") of a 9 x 5 x 5 cm. mass projecting into and filling the right ventricle of an adult patient. In addition, a number of cystic epithelial inclusions have been described in the heart, which may show a superficial resemblance to benign cystic teratoma. Some may come about through isolation of endodermal foci early in embryogenesis, when midline fusion of the paired cardiac

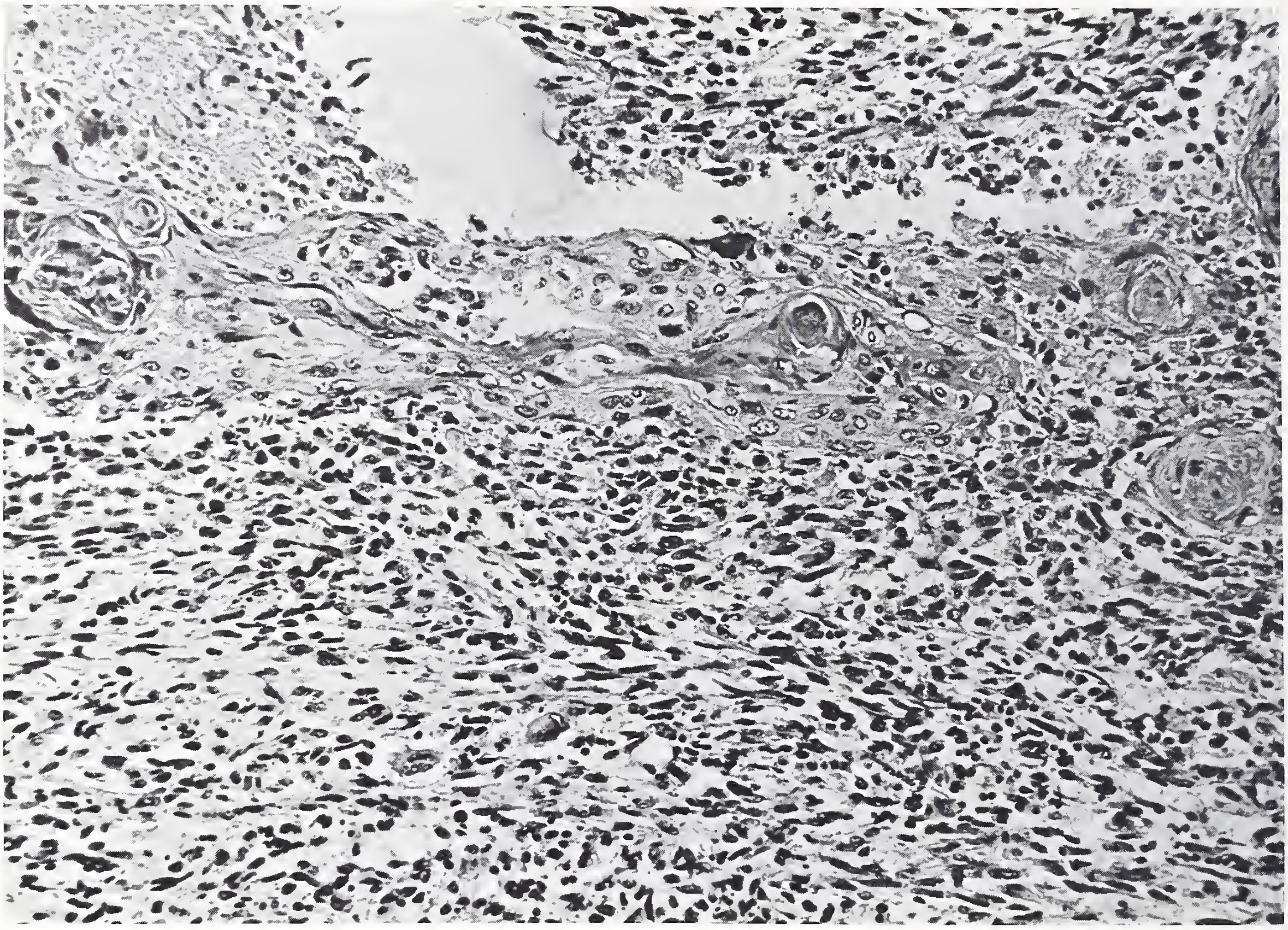

Figure 116
CARDIAC TERATOMA
Epithelial nests with "keratin pearls" within a sarcomatous stroma. X250. (Courtesy of Dr. V. Y. Cabañas, Cincinnati, OH. From Cabañas, V. Y. and Moore, W. M. Malignant teratoma of the heart. Arch. Pathol. 96:399-402, 1973.)

primordia occurs simultaneously with the division of endoderm into foregut and yolk sac (Davidsohn; Leighton et al.). Others are believed to develop from included mesothelial cells, analogous to benign mesotheliomas of the ovaries and testes. For detailed analysis of the structure of these lesions, the reader is referred to the Fascicle on Cardiovascular Tumors by McAllister and Fenoglio. In these lesions, glial cells or primitive neural elements are never found. In spite of the variety of epithelia that may be seen lining the cysts, they lack the mixed organoid nature of teratomas. Except for bronchogenic cyst, attempts at reproduction of complex organ or tissue structures is a characteristic confined to teratomas.

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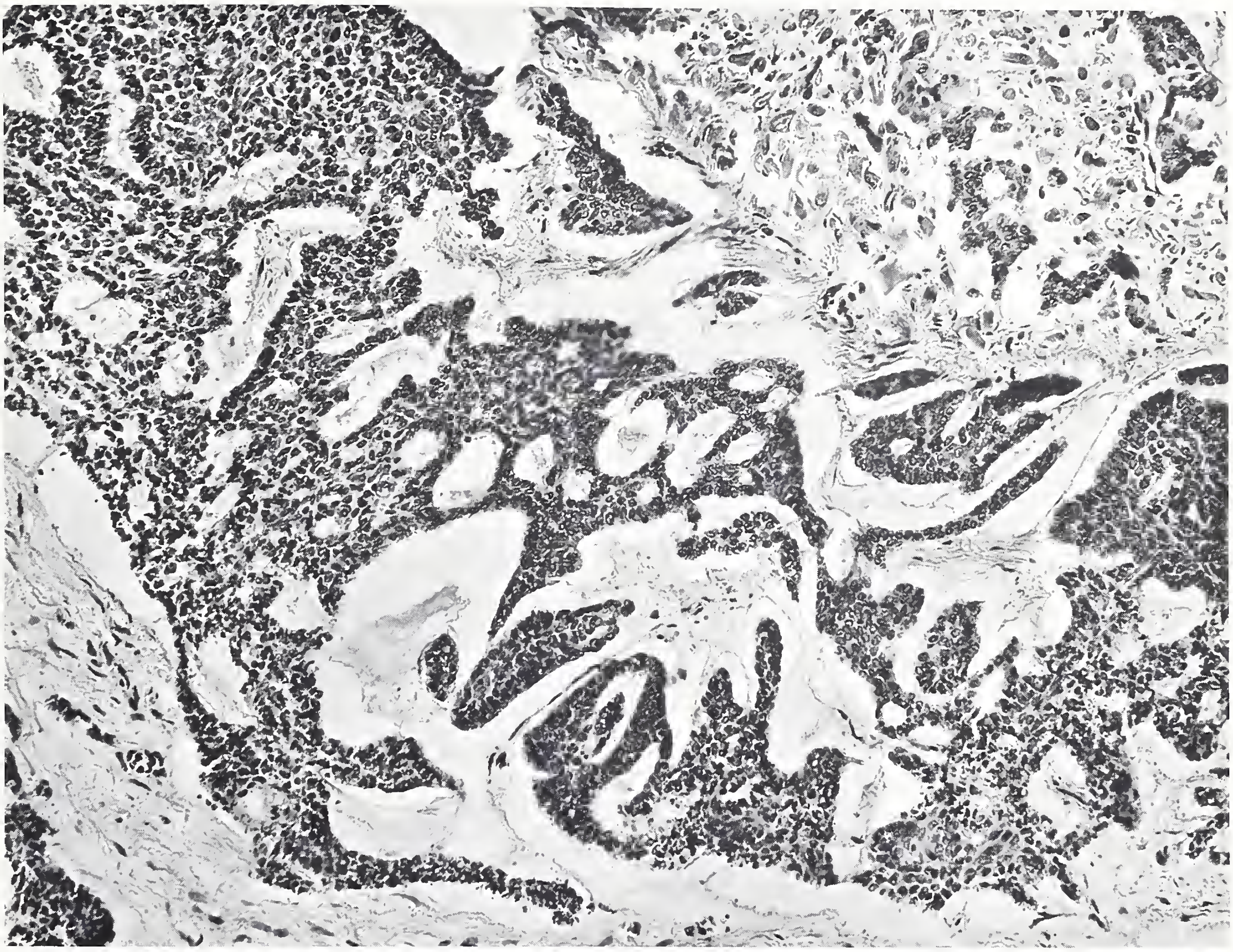

Figure 117

CARDIAC TERATOMA

Small, dark, embryonal-appearing cells arranged in cords and glandlike spaces. This component tissue was found in a metastasis to the vertebral column. X175. (Courtesy of Dr. V. Y. Cabañas, Cincinnati, OH. From Cabañas, V. Y. and Moore, W. M. Malignant teratoma of the heart. Arch. Pathol. 96:399-402, 1973.)

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TERATOMA OF THE LUNG

Collier and associates described, in 1959, a benign teratoma arising from the left upper lobe of the lung in a 46 year old Negro woman. They stated that only 11 teratomas had been described up to that time that were of true intrapulmonary origin. Many of the cases reported as lung teratomas are mediastinal tumors that grow into lung tissue and establish an intimate connection with the latter. Recently it has become apparent that extrathoracic teratomas may metastasize to the lung and simulate a primary lung tumor (Snyder). Hence, both mediastinal and extrapulmonary origin must be excluded before one can accept a diagnosis of teratoma of the lung. According to Gautam, over 20 cases of primary intrapulmonary teratomas were recorded up to 1969. All had occurred in young adults or older individuals, with some predilection for females. The left upper lobe has been the most commonly affected site (Holt et al.). Pound and Willis described a 10 month old male infant with a very large, presumably congenital, pulmonary teratoma. This exceptional case contained embryonal tissues that metastasized to regional lymph nodes from their original primary site in the right lower lobe.

The clinical manifestations have included cough, dyspnea, hemoptysis, and, on occasion, trichoptysis (Laffitte). Association with congenital cardiovascular anomalies has been known to occur (Ali and Wong), although this may be purely coincidental. Because of the extreme rarity of these lesions, the diagnosis is usually made only after the excised specimen is examined. In retrospect, calcification (Trivedi et al.) or cavitation (Bateson et al.) in the x-ray films have been features of diagnostic interest. In a case described by Ali and Wong, an area thought to represent peripheral cavitation corresponded to adipose tissue within the teratoma. Pancreas and thymus are tissues frequently found in these tumors (Holt et al.), a feature that underlines their similarity to mediastinal teratomas and perhaps to a common origin. Pound and Willis believed that the earliest tumorigenic focus developed in the embryonic mediastinum, but that with subsequent growth of the lung bud, the neoplasm is caught up and carried into lung parenchyma. However, some of these tumors have presented as pedunculated endobronchial masses completely covered by bronchial mucosa (Bateson et al.); others, lacking this investment, have shown communication with the bronchial lumen. Pancreatic and thymic tissue have been described in intrapulmonary, bronchus-related teratomas (Holt et al.).

Approximately one-third of the tumors in published cases have been called malignant. Apparently this designation has been used loosely, based on the presence of immature tissues within the tumor, rather than on clear evidence of infiltration and metastases. This practice may account for the unexpectedly good results obtained by surgical treatment of some purportedly malignant lesions (Ali and Wong; Bateson et al.).

Carcinosarcoma and pulmonary blastoma are two lung tumors that exhibit a complex, heterogeneous histologic appearance, and are thus to be distinguished from teratoma. These two lesions were not always well separated from each other in the past; use of the word "embryoma" (Laffitte) further complicated the terminologic confusion, especially since this term was also used, inappropriately in our opinion, to designate teratomas (see Nomenclature).

Carcinosarcoma is a malignant tumor of adult patients, composed of both endodermal bronchial epithelium and mesodermal bronchial connective tissue; as such, the neoplasm is necessarily related to a bronchus (Spencer, 1977). Carter and Eggleston, in the Fascicle on Tumors of the Lower Respiratory Tract, state that to validate the diagnosis of carcinosarcoma, it is necessary to prove that both epithelial and mesenchymal components are malignant. This requirement is fulfilled only by demonstration that both elements have metastasized. The sarcomatous component usually predominates, most often as fibrosarcoma. The epithelial component appears as squamous carcinoma, adenocarcinoma, or large cell undifferentiated carcinoma. Prominent neuroectodermal differentiation is not present in carcinosarcoma, but is the most common form of differentiation in teratomas, and is thus helpful in the differential diagnosis.

Another tumor with dual epithelial and mesenchymal differentiative capacity is pulmonary blastoma (Spencer, 1961, 1977). This tumor has been observed in children as well as adults. In contrast to carcinosarcoma, the neoplastic tissues bear a marked resemblance to the developing lung during its "glandular" stage, or about three months' gestational age. Accordingly, its morphogenesis has been thought to be analogous to that of Wilms' tumor in the kidney. Pulmonary blastoma arises peripherally and does not take origin from large bronchi, although the latter may be compressed when the tumor reaches large dimensions. This location helps to distinguish pulmonary blastoma from carcinosarcoma. Microscopically, pulmonary blastoma may contain primitive mesenchymal components, including areas resembling chondrosarcoma, but the characteristic feature is the formation of tubular structures lined by epithelium and resembling fetal bronchioles. The mesenchyme forms peripheral condensations around these structures. The epithelium may display prominent subnuclear vacuolation and contains abundant glycogen, thus increasing the resemblance with the glycogen-rich bronchial epithelium of the prenatal lung. Spencer (1961) believes that this tumor arises from "pluripotent cells of one germ layer"; he attributed the formation of epithelium-lined tubules to mesoblastic differentiation, analogous to the mesoderm-derived proximal tubules of the kidney. At any rate, neuroectodermal differentiation, usually conspicuous in teratomas but nonexistent or inapparent in pulmonary blastomas, should assist in distinguishing these two tumors. Teratomas, on the other hand, should contain a variety of tissues, indicative of the potential of the parent cells to differentiate along the lines of the three germ layers. When this criterion is applied, it should not be difficult to eliminate from consideration hamartomas and cystic malformations that contain tissues foreign to the lung, such as acinar and endocrine pancreas. Such lesions may be explained as heteroplasia of the embryonic endodermal tissues from which the bronchial system is derived.

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TERATOMA OF THE INTESTINE

The bowel is among the uncommon sites of origin of teratomas. In this location, the tumors adopt the form of cystic tumors filled with sebum and keratinous debris, intimately related to the bowel wall. Differentiation often tends to be almost exclusively in the direction of cutaneous elements, thus accounting for the term "dermoid cyst," under which these lesions are sometimes described (Candreviotis; Gowdy; Palombini et al.). Published reports usually refer to single case observations. A review of available descriptions suggests higher frequency of involvement of female patients, and greater number of distal colonic or rectal localization. However, the cecum (fig. 118), or the small bowel, may be affected (Hafeez et al.; Kay). On occasion, colonic teratomas have appeared as predominantly solid lesions causing intestinal occlusion (Palombini et al.). The age at which these lesions are discovered has varied between 1 and 77 years (Kay; Russell). Unusual complications of these lesions have included associated intestinal adenocarcinoma (Russell) and bilharziasis (El-Katib); in none has there been sufficient reason to believe in other than a fortuitous association. The presence of ova

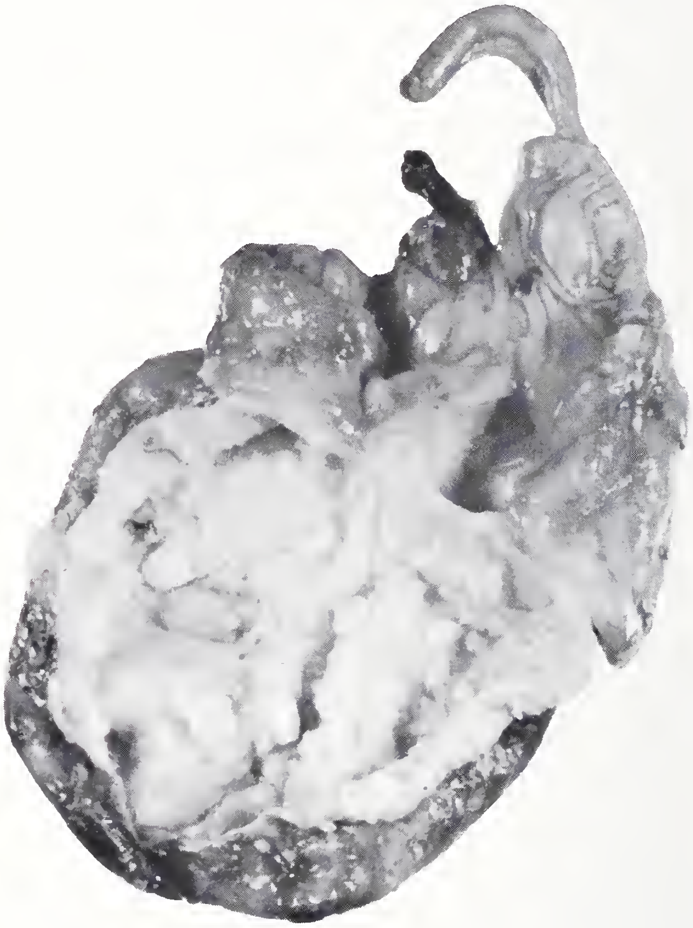

Figure 118
INTESTINAL TERATOMA
A large keratin-filled cyst arises from the medial wall of the cecum. The mass was excised together with the cecum and a portion of the terminal ileum, from a one year old girl. (Courtesy of Dr. S. Kay, Richmond, VA. From Kay, S. Teratoid cyst of the cecum. Digest. Dis. 16:265-268, 1971.)

of Schistosoma in teratomas, although a rare phenomenon, is not confined to rectal teratomas. Schistosoma oviposition has also been noted in ovarian teratomas, retroperitoneal cysts, hydatid cysts, and a cystic teratoma of the umbilical area, as reviewed by Paradinas. In areas where this infestation is endemic, the association may be more prevalent than is generally thought, but there is no evidence in favor of a cause-and-effect relationship between the two diseases.

The differential diagnosis includes presacral teratoma and developmental errors. Some juxtarectal teratomas may be included with teratomas of the sacrococcygeal region, although the latter show a closer anatomic relationship to the sacrum and coccyx, to which they may be firmly adherent, whereas lesions arising from the bowel wall are more closely related to the intestine and often cannot be dissected from the rectal wall (Russell). Maldevelopmental lesions, variously designated "duplications" or "enterocystomas," are similar, and perhaps related, growths. Their distinction from teratomas is based on the uniformity of tissue composition of malformative cysts and the multiplicity of components in teratoma. Failure to discover tissue derivatives of the three germ layers has led some authors to name cysts containing only ectodermal tissues "epidermoid" cysts, and those containing ectoderm and mesoderm, "dermoids" (El-Katib). Indiscriminate use of these terms is not justified. The most prevalent view on nomenclature and classification of epithelial cysts distinguishes dermoids as containing skin and skin appendages, whereas epidermoid cysts are composed of epidermal layers of skin only (Leech and Olafson).

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TERATOMA OF THE SPLEEN

An exceptional case of malignant teratoma of the spleen was reported by Daftary and Barnett in 1970. The tumor presented in a 69 year old woman with abdominal distension and left upper quadrant mass. The 2500 g. spleen had a large (18 cm.) cystic and solid mass. Areas of papillary carcinoma with psammoma bodies, spindle cell tumor, mucus-secreting cells, smooth muscle, and cartilage were identified in this neoplasm. The authors speculated that splenogonadal fusion, an uncommon malformative condition, might sometimes account for the presence of germ cells within the spleen. However, this malformation occurs predominantly in men, and the patient was a female with apparently normal ovaries. The patient died four months after removal of the tumor, and metastases were present in lungs and abdomen, composed of papillary adenocarcinoma and spindle cell sarcoma. The origin of this unique teratoma was uncertain.

Although the clinical diagnosis of splenomegaly imposes the need to rule out a vast number of tumor and nonneoplastic diseases, the histopathologic differential diagnosis is virtually reduced to distinguish between teratomas and true splenic cysts. Cysts of the spleen are usually asymptomatic lesions that present as a palpable mass in the left upper abdominal quadrant of children and adolescents. Of 55 cysts reviewed by Blank and Campbell, more than half occurred in children, although the age ranged between 6 months and 50 years. Males were affected as frequently as females. True splenic cysts, or "primary nonparasitic cysts" are lined by squamous epithelium, in contrast to pseudocysts that lack an epithelial lining. For this reason they have been called "epidermoid" cysts (Blank and Campbell), and sometimes incorrectly referred to as "dermoids" or teratomas. Kissane believes that the squamous epithelium represents squamous metaplasia of an original endodermal or mesothelial lining. Characteristically, the inner surface of splenic cysts is trabeculated by cords and bands reminiscent of the trabeculae carnae of the heart. Their histologic composition is simple in comparison with that of true teratomas.

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TERATOMA OF THE UTERUS

Uterine teratomas, arising away from the gonads, usually on the lateral walls of this organ, pose intriguing questions about the pathogenesis of these tumors. Some examples have originated as small nodules within endometrium (Dallenbach-Hellweg and Whittlinger), accounting for metrorrhagia. The notion that these lesions might represent remnants of a malformed embryo may be discounted on the basis that step-sectioning fails to reveal any traces of placental villi; furthermore, the component tissues usually lie in a completely haphazard way. If displaced embryonic cells from a previous conception were to be the origin of these tumors, it would be necessary to account for their final location by postulating that they traversed the chorion (Mold). Usually, the differential diagnosis presents no major difficulty. It is necessary to recall, however, that fetal parts may survive in the uterus after accidental displacement (Newton and Abell), and that some heterotopic tissues may come to lie in this site through metaplasia (Roth and Taylor; Urbanke; Zettergren) of normal cells. Müllerian embryonic remnants have been held responsible for the laterality of uterine teratomas, but this is pure speculation (Mold).

Malignant mixed müllerian tumors (MMT) of the uterus constitute a well recognized entity comprising 1-2 percent of all uterine cancers, and are known to contain both carcinomatous and sarcomatous tissues (Barwick and LiVolsi; Kempson and Bari). These tumors should be distinguished from teratomas. MMT may be of "homologous" type, if the tumor reproduces tissue intrinsic to the uterus, or "heterologous" type, if the mesenchymal portions have differentiated into sarcomas resembling tissues extrinsic to the uterus, such as bone, cartilage, and striated muscle. Admixed with the prominent sarcomatous areas are found foci of carcinoma, which may adopt the form of squamous carcinoma, adenocarcinoma, or adenoacanthoma. Thus, these tumors constitute examples of "carcinosarcoma," although growing imprecision in the use of this term has resulted in recent pleas for its proscription from current terminology (Barwick and LiVolsi; Kempson and Bari). MMT arise predominantly in postmenopausal women who often give a history of previous radiation to the involved area (Kempson and Bari). In contrast, teratomas of the uterus have been described in women of reproductive age; their histologic appearance has shown fully mature tissues with organoid differentiation, and a wide diversity of tissues has been present, representing derivatives of the three germ layers. In keeping with the innocuous histologic appearance of uterine teratomas, their clinical behavior has been uniformly benign.

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TERATOMA OF THE UTERINE TUBE

Primary teratomas of the uterine tube are extremely uncommon. Mazzarella and associates reviewed the literature in 1972 and found 43 reported patients whose ages varied from 21 to 60 years, with highest frequency in the third decade. Symptoms included abdominal pain, dysmenorrhea, and bleeding. No patient was diagnosed preoperatively. Most tubal teratomas arose in the isthmus or ampulla; some were pedunculated and projected into the tubal lumen. Sizes varied between 0.7 cm. and 20.0 cm. in diameter, with a mean of 5.7 cm. Twenty-one tumors were on the right, 14 on the left, and 5 were bilateral. Twelve tumors occurred in nulliparous women, and 13 tumors in women with one or two previous pregnancies. In the remainder, the obstetric history was not known. All but one of the reported tumors were clinically and histologically benign; the exception was a tubal teratoma considered to be malignant because of the presence of neuroblastic tissue. The tumor was confined to the uterine tube of a 22 year old nulligravida (Sweet et al.).

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TERATOMA OF THE RETROUTERINE CUL-DE-SAC

This localization is most unusual. Wheeler described the case of a 25 year old woman. The tumor gave rise to extensive seeding of mature glial nodules in the peritoneum, in a manner analogous to the better known examples of ovarian teratomas with peritoneal gliomatosis. The quoted neoplasm, however, showed no relationship to the ovaries, and arose entirely from the cul-de-sac (fig. 119).

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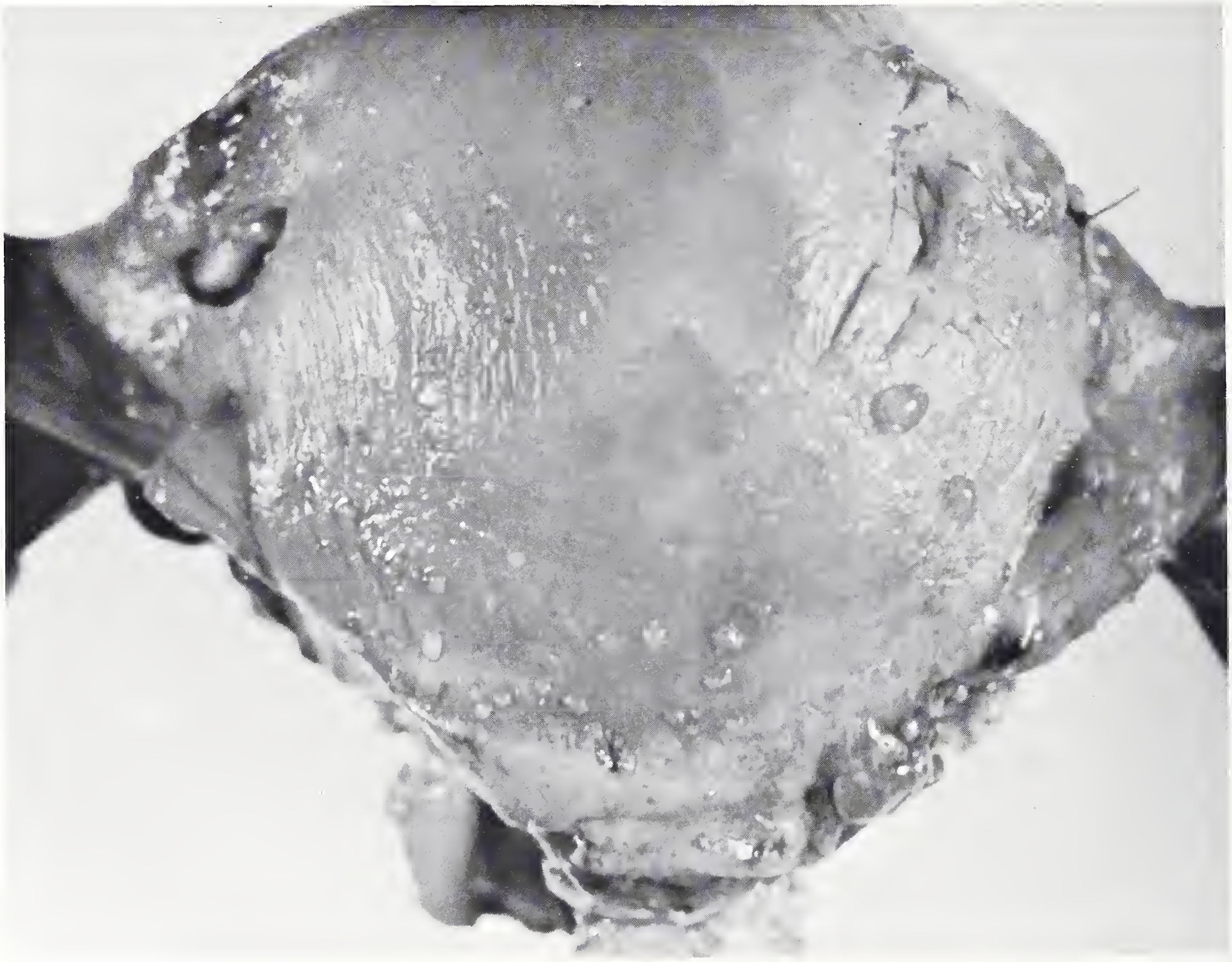

Figure 119
RETROUTERINE CUL-DE-SAC TERATOMA
Gray, translucent glial implants on the posterior surface of the uterus. (Courtesy of Dr. J. E. Wheeler, Philadelphia, PA.)

TERATOMA OF THE KIDNEY

Very rarely teratomas can arise within the kidney. One such tumor was reported by Dehner in a 5 month old female infant. Dehner reviewed the available literature up to 1973, and was able to accept only two previously reported cases as true teratomas originating within the kidney parenchyma. In 1978, Aubert and Casamayou reported one case and reviewed six others. The intrarenal teratoma reported by Dehner was stated to be clinically, radiologically, and macroscopically indistinguishable from a Wilms' tumor, regardless of the previous experience of the observers. This emphasizes the need for histopathologic confirmation before initiation of any form of therapy that may be hazardous to the patient. On the other hand, distinction between teratoma and Wilms' tumor may not be as straightforward as it is often assumed, even after histologic study.

The prevailing concept of the histogenesis of Wilms' tumor maintains that this neoplasm derives from the mesodermal metanephrogenic blastema. Accordingly, it is not surprising to find Wilms' tumors constituted of primitive blastema cells, tubular epithelium, and/or glomerular formations. Islands of cartilage, adipose tissue, fibrous tissue, and striated muscle cells are usually considered "acceptable" derivatives of the metanephrogenic blastema. Thus, the presence of these tissues contributes to the composite histologic appearance of some nephroblastomas, but does not challenge the most widely accepted concept of the histogenesis of Wilms' tumor. On occasion, however, nervous tissue has been observed in otherwise typical Wilms' tumor. Bannayan and associates reported ganglionic cell differentiation in the pulmonary metastases of a Wilms' tumor following radiotherapy. Kuo illustrated neuroectodermal derivatives in a Wilms' tumor found in a female infant with horseshoe kidneys, and discussed the implications of this finding for the histogenesis of nephroblastoma. Dische and Johnston described a neoplasm which they classified as intrarenal teratoma, arising in a premature female infant of 38 week gestational age. This infant showed numerous congenital anomalies, including horseshoe kidneys and midline fusion of the adrenals. The histologic appearance of the tumor was similar to that of the neoplasm illustrated by Kuo. Hence, it appears that, in addition to renal tubules, glomeruli, cartilage, and muscle, some renal tumors are capable of aberrant differentiation into glial tissue and ganglion cells. We interpret as nephroblastoma those tumors that, were it not for a neuroectodermal component, would have been unquestionably classified as Wilms' tumor. Their teratomatous nature seems precluded by the absence of endodermal derivatives (Kuo) as well as by the overall histologic resemblance to nephroblastoma. Without giving details, Willis had noted the presence of Wilms' tumor in a patient with horseshoe kidneys.

In adults, teratoma of the kidney has been reported rarely. Kojiro and associates described a primary renal teratoma in a 40 year old patient. The tumor contained areas of carcinoid tumor, but the patient showed no manifestations of the carcinoid syndrome. Hamvasi and co-workers described a 71 year old male with a malignant teratoma that originated in the right kidney which also had a double ureter. The tumor showed atypical cartilage, bone, spindle cell sarcoma areas, and areas of carcinoma resembling hypernephroma. In contrast, renal teratomas occurring in children have had a benign clinical course, in spite of a histologic composition that included immature neuroectodermal components (Aubert and Casamayou). However, the number of reported cases with adequate follow-up is too small to justify any general statements in this regard.

The proximity of the gonadal ridge and the nephrogenic anlage in the embryo may explain the presence of abnormally displaced germ cells within the kidney. Propinquity between these two embryonic formations is so great that it is surprising that tumors derived from germ cells, including teratomas, should occur so uncommonly in the kidney. We are aware of two well authenticated cases of yolk sac tumor arising within the kidney (unpublished observations) of adult individuals in whom a primary gonadal tumor was reasonably well excluded.

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SOME TERATOMAS IN ANIMALS: SPONTANEOUS AND INDUCED

TERATOMAS IN THE MOUSE

Spontaneous Teratomas

Spontaneous development of teratomas in most laboratory mice is a very rare occurrence: one ovarian teratoma was found in 22,000 autopsies of female mice, and not a single one in 19,000 male mice (Slye et al.). However, since these older studies, several teratomas have been described, all within the genital system (Fawcett), and certain strains of mice have been developed for experimental studies (Stevens and Little). Thiery described two cases of ovarian teratoma found in a colony of 2000 animals of the C3H/N strain (incidence of 0.1 percent). One of these was a solid, histologically benign teratoma without grossly cystic components.

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The LT/Sv Mouse

Inbred mice of the LT/Sv strain are known to develop teratomas spontaneously with high frequency. By 90 days, 50 percent of the female animals have ovarian teratomas. About 10 percent of the virgin female mice of this strain, when autopsied, are found to be pregnant. Eggs divide by parthenogenesis and implant in the uterus, but the majority are aborted by 5-7 days of gestation. In the ovary, eggs that undergo parthenogenesis develop to resemble normal embryos up to 7.5 days of gestation; thereafter they become disorganized and transform into well differentiated teratomas, most of which are largely visible, although some are discovered only on microscopic examination of the ovary. A small number become poorly differentiated malignant teratomas (Stevens).

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Embryo-derived Teratomas

Teratocarcinomas may be produced experimentally by grafting early embryos to various anatomic sites of adult mice. The resulting teratomas are for the most part well differentiated; occasionally they are malignant, as defined by their morphologic and retransplantability characteristics. Favored sites for the transplant are the kidney and the testis. Only presomitic transplanted embryos can give rise to a fast-growing, retransplantable (malignant) teratoma. These tumors invade locally and kill the host by producing emaciation, but they do not metastasize. C3H, A, and CBA are mouse strains capable of developing the tumors; other strains are apparently resistant. After 8 days of gestation, a transplanted embryo will not produce a teratoma regardless of the site in which it is implanted. There is no morphologic difference between spontaneous testicular or ovarian teratomas and embryo-derived teratomas in mice (Damjanov and Solter).

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TERATOMAS IN RATS

To our knowledge, spontaneous teratomas in the rat have been reported only once (Schardein and Fitzgerald). However, different parts of the rat embryo have been transplanted to extrauterine sites in connection with studies on cytodifferentiation, and large masses of chaotically disposed tissues have been obtained.

Nicholas and Rudnick transplanted rat egg cylinders to the chick chorioallantoic membrane (CAM). Rat embryo heterografts on CAM keep poorly, and only for a limited period of time, thereby interfering with studies of cytodifferentiation. However, transplantation of 7.5 to 9 day old rat embryos under the kidney capsule of adult, random-bred or inbred Fischer rats can be maintained for several months, producing tumors that weigh up to 30 times the weight of an adult rat kidney (Skreb et al.); the anterior chamber of the eye has also been used successfully as a recipient site (Levak-Svajger and Skreb). Uncontrolled growth of poorly differentiated cells (teratocarcinoma) occurs very rarely, in comparison with the grafts of mouse embryo. On the other hand, retransplantability characteristics in the rat have not been studied to a comparable extent. The differentiation of the grafted rat embryo cells is influenced not only by the characteristics of the recipient site, but by the developmental stage of the transferred embryo. Different tissues in organotypic arrangement are developed depending on the part of the egg cylinder that is grafted.

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TERATOMAS IN GUINEA PIGS

A thorough review of the literature on tumors of guinea pigs was undertaken by Rogers and Blumenthal in 1960. They noted that tumors arise only rarely in these animals below the age of 3 years; at the time of the review, a total of 138 tumors, of which 3 were ovarian teratomas, had been described. In 1970, Vink reviewed the subject and brought the number of ovarian teratomas in guinea pigs to 13. Mosinger suggested a parthenogenetic development of oocytes as a cause of ovarian teratomas, and based his suggestion on observations of early division of unfertilized ova. A variety of tissues are present in these tumors, the most prominent of which is neural tissue in various degrees of maturity. Willis described two ovarian teratomas, one of which had given rise to peritoneal neuroglial implants.

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TERATOMAS IN THE HORSE

The existence of spontaneous teratomas in horses is well documented. These tumors occur predominantly in the ovary, testicle, or subcutaneous region (figs. 120, 121). A special tumor is seen in the temporal region that displays dental elements and is often called "temporal odontoma." Its teratomatous character is incompletely documented in some reports. Clinically, these tumors manifest with discharge at the base of the ear and swelling anteroventral to the external auditory meatus. In the absence of dental components, surgical treatment is easily accomplished. However, when teeth are present, usually resembling molars, there may be deep attachment to the underlying temporal bone, and the morbidity and mortality related to excisional attempts is correspondingly enhanced (Mason). Testicular teratomas in the horse are usually benign, well differentiated tumors (Moulton). Most commonly they appear in the 1 to 5 year old animal, but since domestic animals are usually brought to veterinary clinics for castration at a young age, bias in selection may account for the greater frequency in young animals. Vaughan considered testicular tumors to be more common in the older horse. Cryptorchidism frequently occurs in the horse, but teratomas have been reported in the cryptorchid or in the descended testis (Smyth).

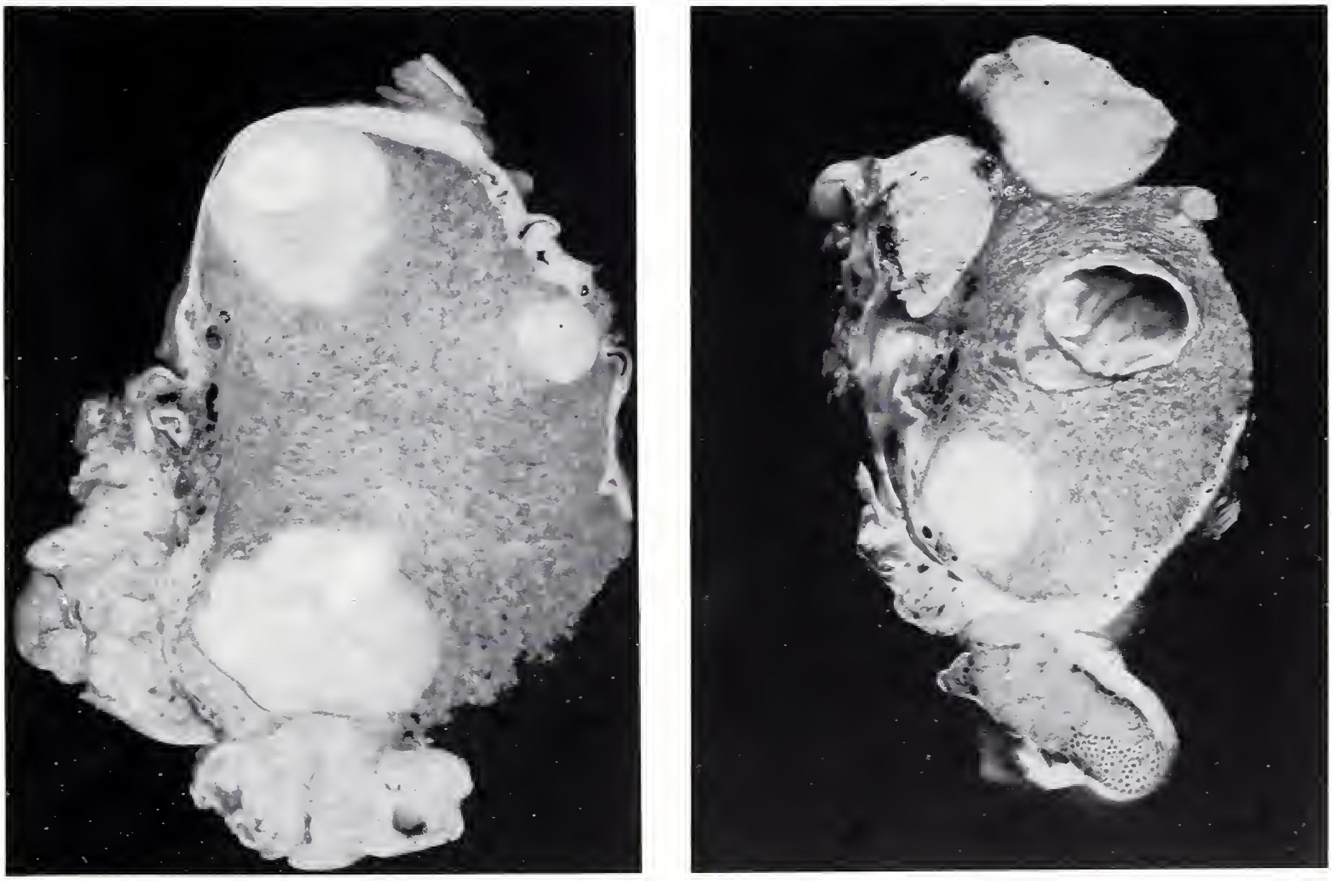

Figure 120
TERATOMA IN HORSES
Multiple bilateral teratomas in a horse's testis. (Also fig. 1A-B, Fascicle 9, First Series, Teratomas. Atlas of Tumor Pathology.)

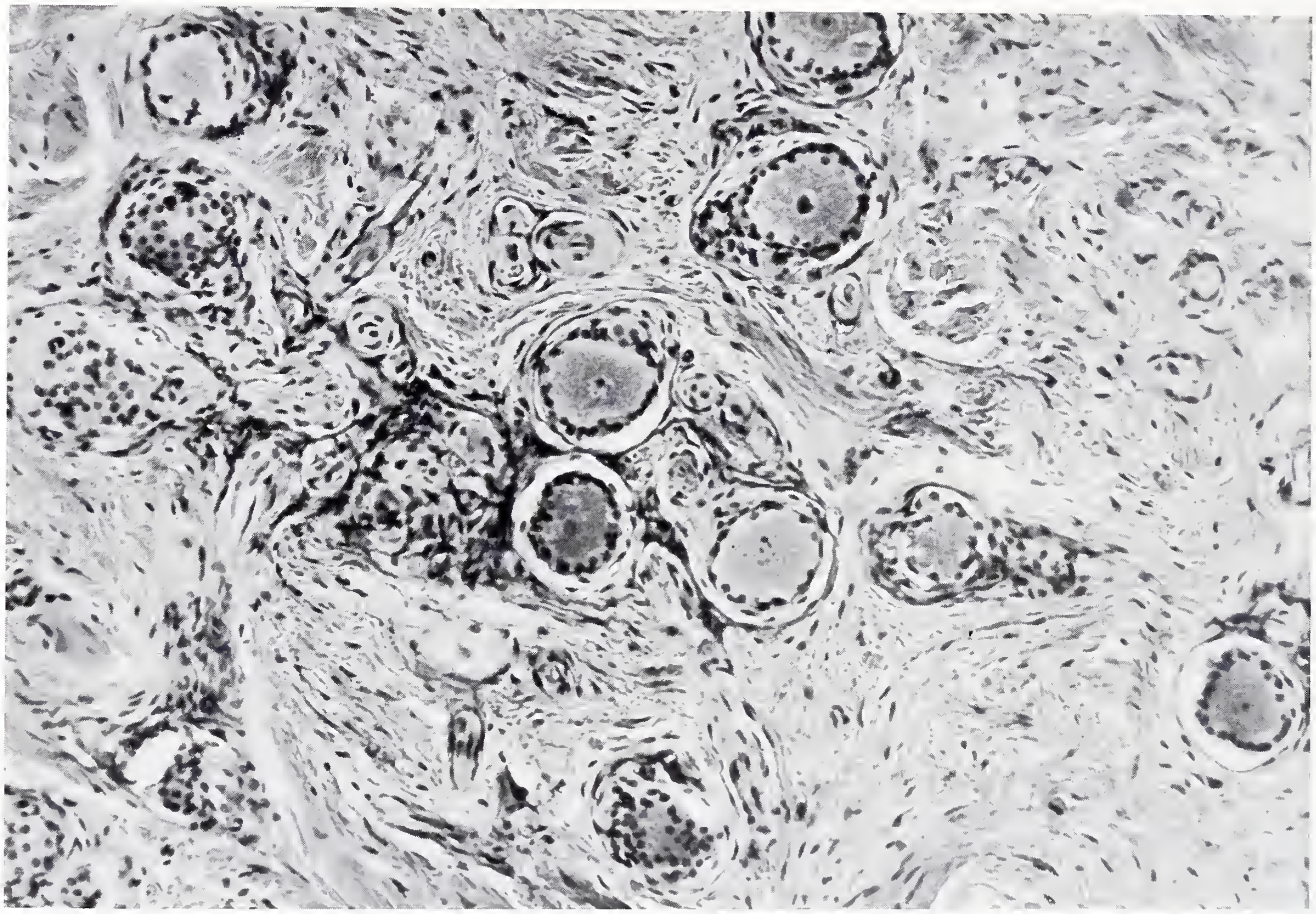

Figure 121
TERATOMA IN HORSES
Sympathetic ganglionic tissue in a teratoma of a horse's testis. X144. (Also fig. 25, Fascicle 9, First Series, Teratomas. Atlas of Tumor Pathology.)

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TERATOMAS IN DOGS

Dogs are extensively used in research, and possibly no other animal has a longer history of continuous association with man as a pet. By the light of these facts, the rarity of reported canine teratomas is striking; apparently no testicular teratomas are on record in this animal, and ovarian teratomas are very uncommon. Canine ovarian neoplasms make up between 0.7 percent and 1.2 percent of all canine tumors; of these, only an occasional case is a teratoma (Clayton; Cotchin; Dehner et al.). Ordinarily, the teratomas of the canine ovary are benign. A malignant case was reported by Clayton, in which the metastases were composed of mesenchymal cells. Two extensively metastasizing malignant teratomas of the ovary have been well described: one in an adult (9 year old) German Shepherd, and the other one in a young Bull Mastiff. "Embryoid bodies" and anaplastic epithelial cells were noted in the mestastases (Patnaik et al.).

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TERATOMAS IN MONKEYS

Macacca mulatta, the rhesus monkey, is extensively used in biomedical research, yet the number of teratomas reported in this animal remains very low. Rohovsky and coworkers could find only three described instances of benign ovarian teratoma up to 1977, to which they add two further observations. These corresponded to benign cystic teratomas ("dermoid cyst") with derivatives of the three germ layers; in one of these cases the normal number of chromosomes was present in cultured teratoma cells.

Gubern Salisachs and Gubern have illustrated a congenital sacrococcygeal teratoma in a newborn chimpanzee. They examined various aspects of the ontogeny and phylogeny of the sacrococcygeal region, and hypothesized that the vulnerability of this anatomic area to the inception of teratomas is related to the disappearance of a tail in evolution. Sacrococcygeal teratomas, according to these authors, do not occur in tailed mammals, but only in those whose caudal appendix normally involutes during embryogenesis. Such teratomas, in their colorful expression, are "the price we pay for the biped upright posture."

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TERATOMAS IN BIRDS

A possible counterpart of human "dermoid cyst" has been found in chickens: a feather-containing cystic structure was described adjacent to the liver, in the greater abdominal air sac of an 8 week old pullet (West). Structures derived from ectoderm and mesoderm were identified in its wall. Similarly, spontaneous gonadal or extragonadal growths occur in domestic fowl that may be compared to human teratomas (Campbell and Appleby; Helmboldt et al.; West). Interest in avian models of experimental teratomas dates back over 50 years, when injection of zinc salts was first shown to produce testicular teratomas in the testes of roosters (Michalowsky, quoted by Guthrie). Copper and cadmium were later shown to have the same effect: Guthrie has induced testicular teratomas in the Japanese quail by injection of 3 percent zinc chloride soluble in water, at pH 3.2, followed by increased photoperiodic stimulation with artificial light. With this method it was possible to produce testicular teratomas in the quail (*Corturnix coturnix japonica*) during the season of the year at which the gonads are least susceptible to teratoma induction by metallic salts. Photostimulation is thought to increase the gonadotrophic output of the avian anterior pituitary.

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TERATOMAS IN HELMINTHS

Maldevelopmental processes in helminths have been interpreted as teratomatous. Johnson and Viglierchio described an abnormality in the moulting process of *Heterodera schachtii*, a plant beet cyst nematode parasite treated with a sesquiterpene derivative (2,3-cis/trans 6,7 trans farnesy/diethylamine). Testicular enlargement and a "male-like" inclusion within a larva were obtained after this treatment, presumably as effects of the chemical upon primordial germ cells of the nematode.

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